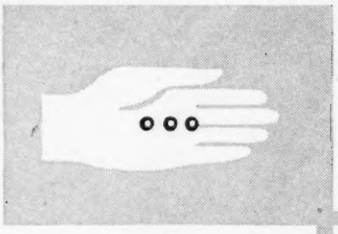
The American Journal of Medicine

March 1947

THE YORKE PUBLISHING COMPANY, INC.
49 WEST 45TH STREET • NEW YORK 19, N.Y.

The American Journal of Medicine

The American Journal of Medicine is published monthly by The Yorke Publishing Co., Inc., 49 West 45th Street, New York 19, N. Y. Yearly Subscription, $10.00 U. S. A.; $12.00 Canada; $12.00 Foreign. Single Numbers $2.00; Special Numbers $4.00. Entered as Second Class Matter June 28, 1946, at the Post Office, New York, N. Y., and on June 28, 1946, at York, Pa., under the act of March 3, 1879. March, 1947—Volume II, No. 3.



$$(C_5H_{11}O_5COO)_2\,Fe \rightleftharpoons Fe^{++} + 2\,C_5H_{11}O_5COO^-$$

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FOR HYPOCHROMIC ANEMIAS

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FERGON, by its chemical nature, is inherently agreeable iron. Only slightly ionized, free of precipitating action on proteins,[1] ferrous gluconate is non-astringent, non-irritating, essentially free from gastro-intestinal distress.

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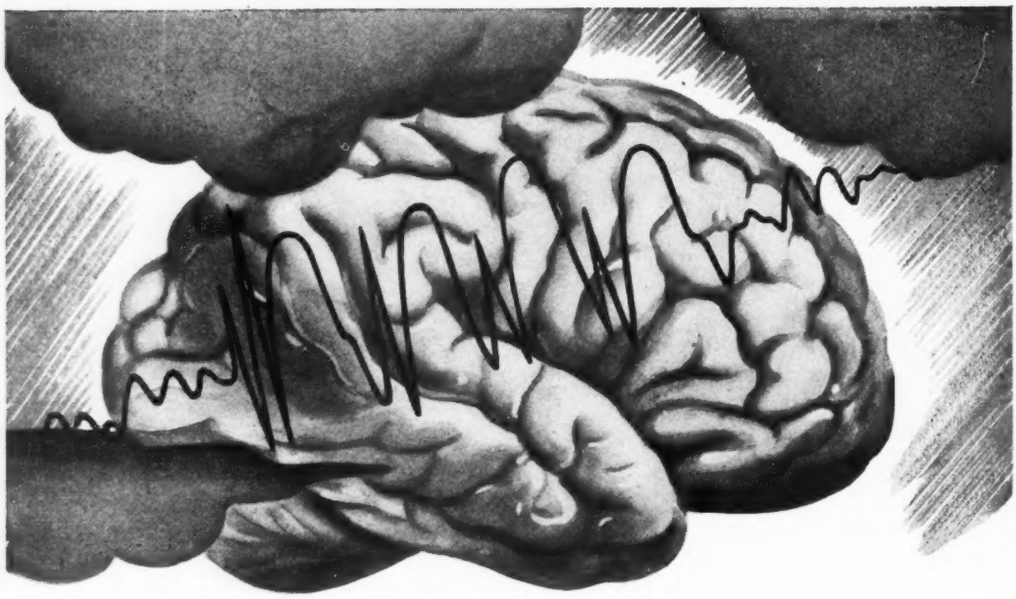
1. Reznikoff and Goebel: J. Clin. Investigation 16:547, 1937.
2. Editorial: J.A.M.A. 127:1056, 1945.
3. Thompson: Biochem. J. 34:959, 1940.



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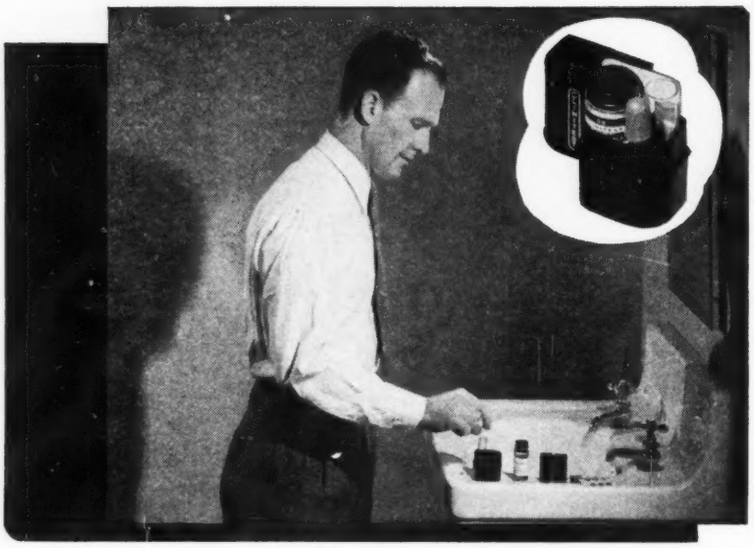

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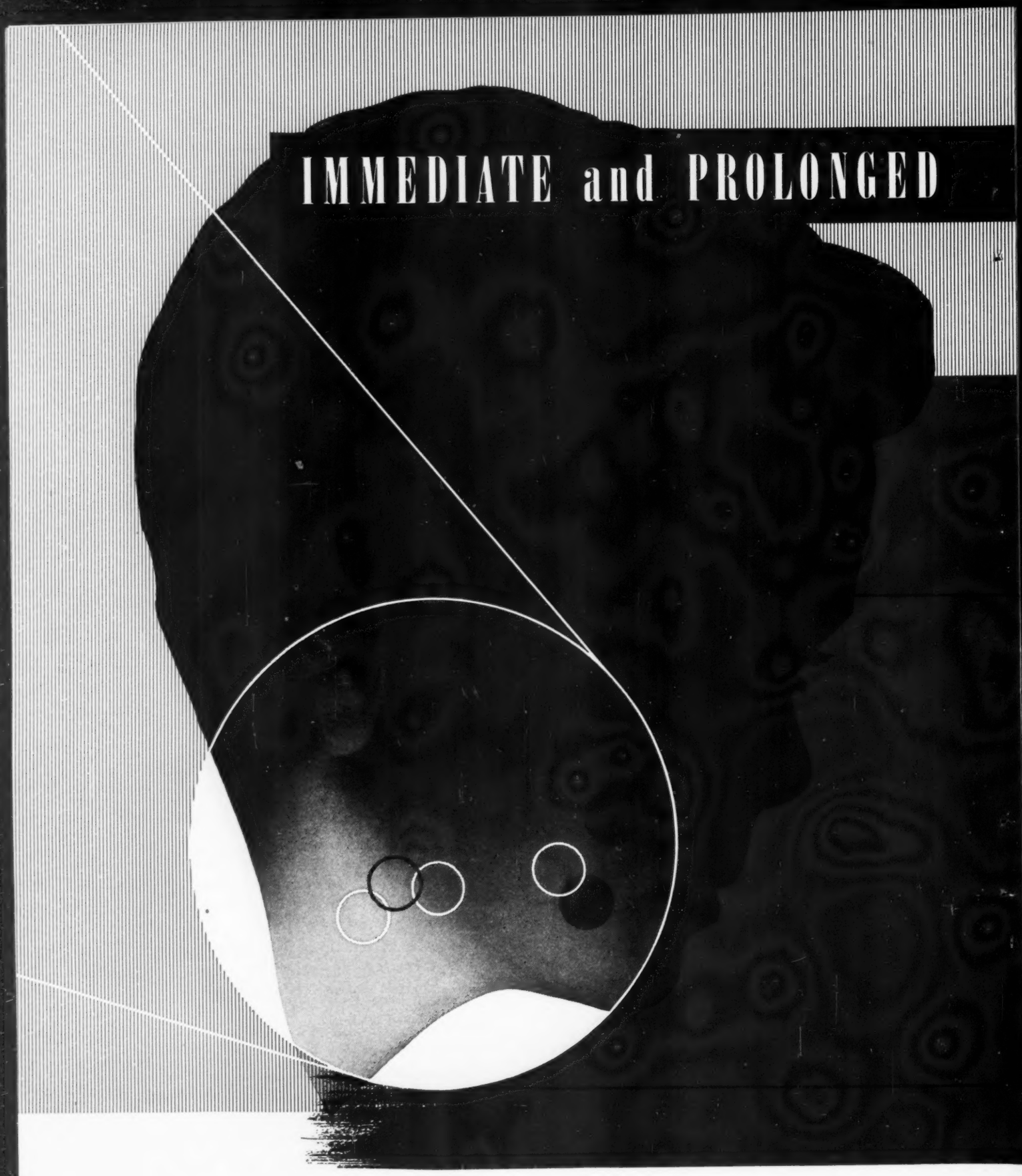

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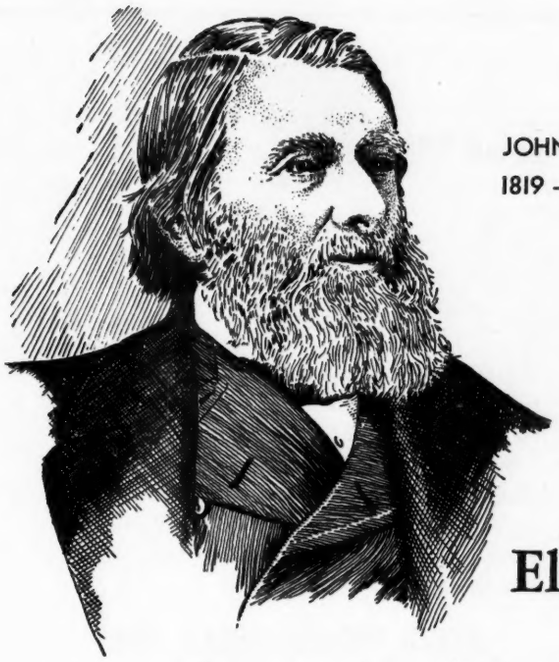

JOHN RUSKIN
1819 - 1900

Ruskin . . . *and the* Cambridge Electrocardiograph

A Doctor recently sent us the quotation from Ruskin which we print below. He commented that although written long before the age of Electrocardiography, this philosophy is indeed pertinent today and applies generally to medical equipment and particularly to Electrocardiographs:

"There is hardly anything in the world that some man cannot make a little worse and sell a little cheaper . . . It's unwise to pay too much, but it's worse to pay too little. When you pay too much, you lose a little money—that is all. When you pay too little, you sometimes lose everything because the thing you bought is incapable of doing the thing it was bought to do. The common law of business balance prohibits paying a little and getting a lot. It can't be done."

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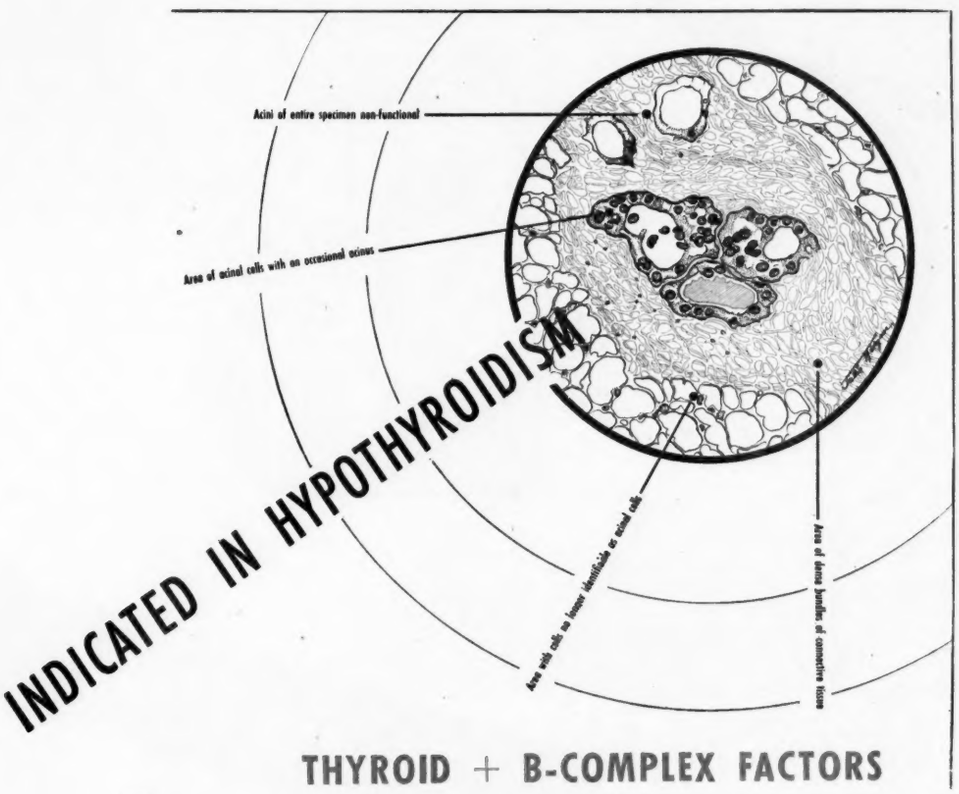

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EACH TABLET CONTAINS:
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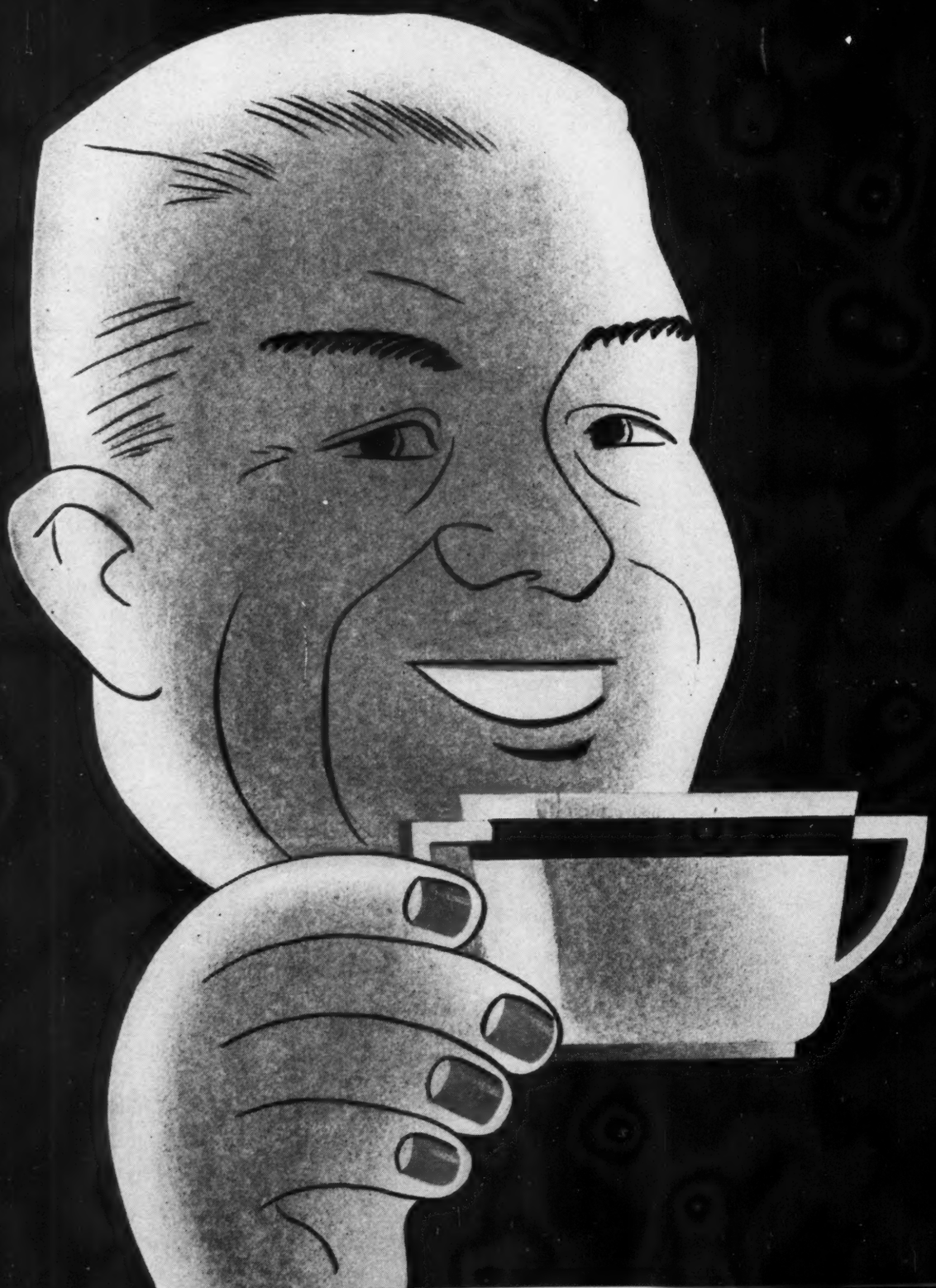
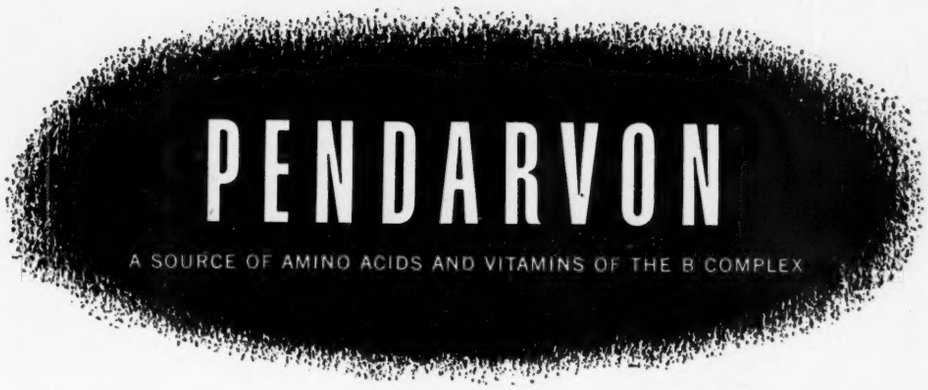


with well-balanced and palatable



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*Ruskin, S. L.: The Role of the Coenzymes of the B Complex Vitamins and Amino Acids in Muscle Metabolism and Balanced Nutrition, Amer. J. Dig. Dis., *13*:110-122 (April) 1946.

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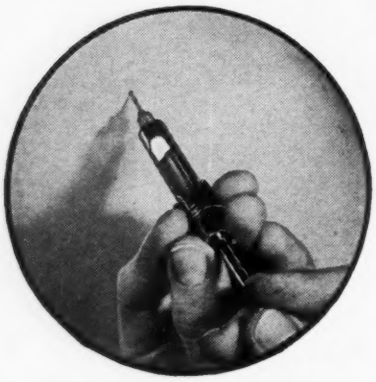
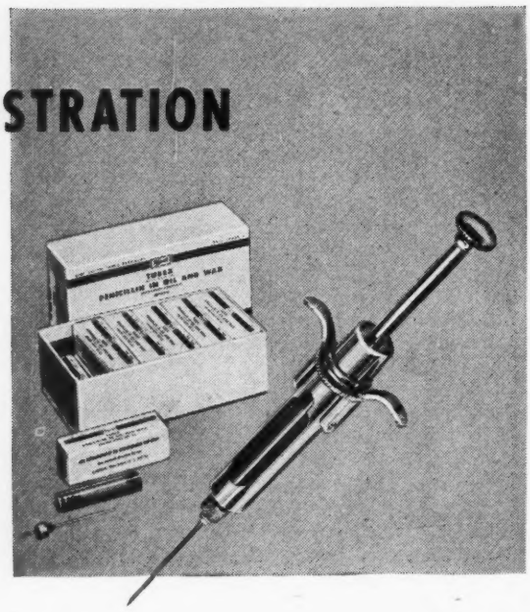


Before injecting aspirate to insure that needle is not in a blood vessel.



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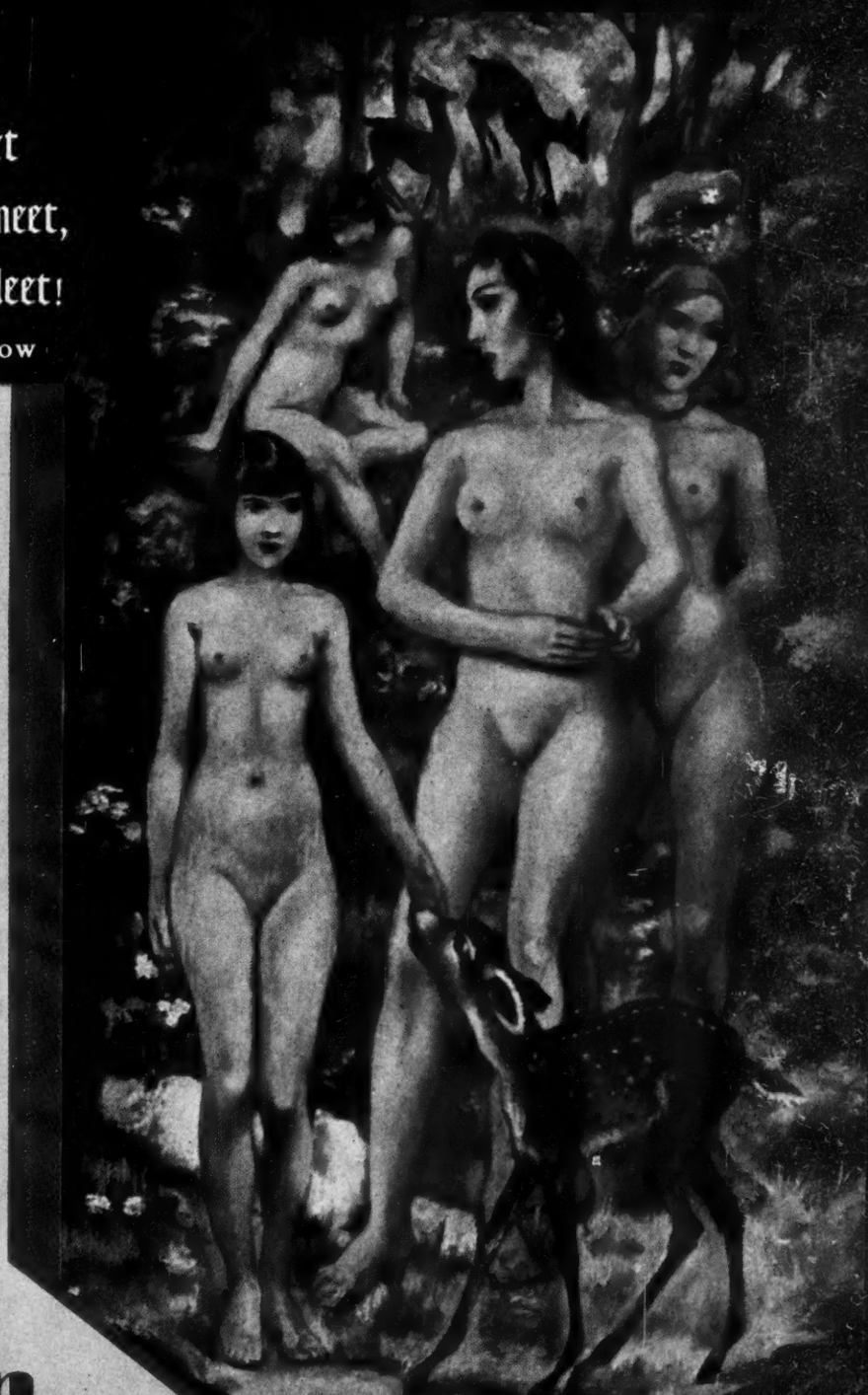
Standing, with reluctant feet
Where the brook and river meet,
Womanhood and childhood fleet!

—LONGFELLOW



IMPROVED medical care, giving assistance through the labyrinth of the difficult adolescent years, is a foremost achievement of modern medicine. Greater promise for the future is the heritage of American young womanhood, as a direct result of translating the achievements of medical research into successful guidance of the adolescent toward normal maturity. In the advance toward this goal the endocrinologist has made some of the greatest specialized contributions. Proper use of the hormone preparations now available to every physician is a priceless part of today's superior medical care. Lively interest in research and long experience in production have made Ciba hormone products leaders in this field.

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1. Greene, R. R.: Int. Abst. Surg., 74: 595, 1942

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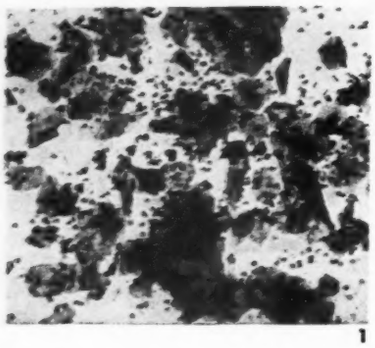
Ovocylin Suppositories in Children's size, 0.04 mg. concentration, boxes of 30. Adult's size, 0.04 and 0.4 mg. concentrations, boxes of 10.



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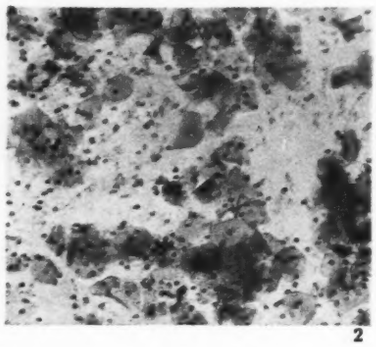

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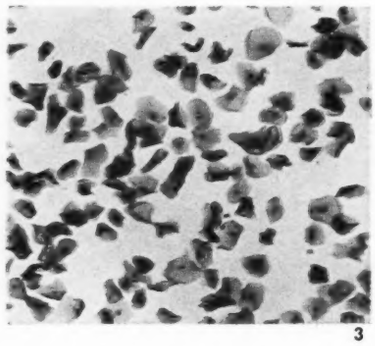


3

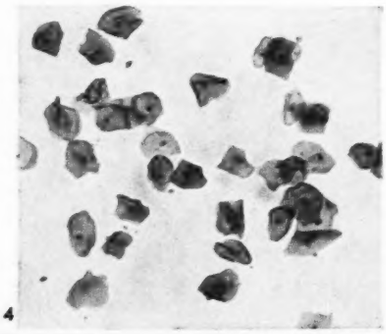
Vaginal Smears Demonstrate Effect of Estrogen Therapy

ONE. The vaginal smear in untreated menopause shows a severe estrin deficiency, preponderance of leukocytes and atrophy of the vaginal mucosa.

TWO AND THREE. These smears demonstrate the effects of partial estrin replacement therapy during treatment. The smears appear clearer, diminished leukocytes, some cornification.

FOUR. The effects of full estrin replacement therapy in the menopause. The smear appears clean and free of leukocytes, large irregular cornified cells with pyknotic nuclei.

Microscopic slides from Dr. E. Kost Shelton, Shelton Clinic, Los Angeles, Cal.



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The American Journal of Medicine

VOL. II MARCH, 1947 No. 3

Streptomycin Treatment of Urinary Tract Infections*

With Special Reference to the Use of Alkali

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THERE are a number of reports on the streptomycin treatment of urinary tract infections caused by susceptible gram-negative organisms.[1–9] The clinical results have been quite variable. Some authors have advocated alkalinization of the urine during streptomycin therapy,[8,10,11] but to date there have been no convincing data to indicate that the clinical results of streptomycin therapy are favorably influenced by alkalinization of the urine. The purpose of this report is to present clinical and bacteriological observations in twenty-one streptomycin-treated patients with urinary tract infections, of whom fourteen were also treated with alkalis.

CASES, MATERIALS AND METHODS

Case Selection. Adult patients with urinary tract infections were selected for streptomycin treatment because other forms of therapy either had failed or seemed undesirable for them. The organisms isolated from cultures of the urine were proved first to be susceptible to the action of streptomycin, *in vitro* and, in most cases, to be inhibited by the concentration of the antibiotic expected in the blood and urine. One or more courses of sulfonamide drugs had been given to sixteen patients prior to streptomycin treatment and the infection persisted in eleven of these cases in spite of an adequate course of the sulfonamides. In the remaining five patients, sulfadiazine therapy was started, but was soon discontinued either because of sensitivity reactions (two cases) or because of poor excretion of the drug (three cases). Sulfonamides were withheld from three patients who had hypertensive cardiovascular disease and from one who had congestive heart failure. Penicillin had been given to ten patients, methenamine to four and mandelic acid to one, without response in each instance.

The approximate duration of infection was known in seventeen cases: ten had infection of a year's duration or longer, two had had urinary symptoms for a period of between six and twelve months. In four patients the onset of symptoms was about two months before the streptomycin treatment and one patient had an infection of only two weeks' duration that proved unresponsive to both sulfadiazine and penicillin. The remaining four patients had chronic infections, the duration of which could not be determined. Retrograde pyelograms had been done in eleven of the patients and anatomical abnor-

* From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) and the Mallory Institute of Pathology, Boston City Hospital and the Department of Medicine, Harvard Medical School. The streptomycin was provided by the National Research Council from supplies assigned for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents. These studies were aided, in part, by a grant from the United States Public Health Service.

malities were demonstrated in ten of them. Dilated pelves or ureters were found in five cases, slight dilatation of the minor calyces in one and renal stones in three. One patient had a spina bifida and loss of sphincter control and cystoscopy in that case showed a dilated bladder and a urethral diverticulum containing a stone. Diminished renal function was found in seven patients. In three of these patients it was probably the result of the infection while in the other four it was associated with hypertensive cardiovascular disease. The remaining patients showed no functional renal abnormality.

Bacteriological Studies. Cultures of the urine were made in liquid media and on the surface of solid media before, during and after the streptomycin treatment. Agar pour plates of 10-fold dilutions of the urine were also made in most cases in order to quantitate the numbers of bacteria present. Blood cultures were done in almost every case but only those in Case 15 were positive. All of the different strains of bacteria encountered were isolated in pure culture on streptomycin-free media and then preserved in the frozen state so that the morphological, cultural and biochemical characteristics of the organisms isolated at different times from the same patient could later be compared under nearly identical conditions.*

Sensitivity of the Strains.† Tests for sensitivity were carried out with cultures derived from single colonies of the organisms grown in brain heart infusion broth (Difco), pH 7.4, and the same medium was used for diluting both the organisms and the streptomycin. Equal volumes of a 10^{-4} dilution of culture containing approximately 100,000 organisms were added to serial 2-fold dilutions of streptomycin and incubated for twenty-four hours. Tubes in which there was no visible growth were then subcultured to streptomycin-free nutrient agar and incubated for twenty-four hours longer. The sensitivity was considered to be the minimum concentration of streptomycin (M.I.C.) in which there was no growth in the broth and on the agar. The broth used for the inoculum also contained 1 per cent defibrinated horse blood which served as an indicator of growth. Control observations showed that this amount of blood neither stimulated growth of the standard strain nor inhibited streptomycin action in this medium. A type A Friedländer's bacillus, strain T, used as a standard in this laboratory was always included as a control. This organism is inhibited by 0.78 units but not by 0.39 units of streptomycin.

Streptomycin Levels. The concentrations of the streptomycin in blood and urine were determined by a dilution method similar to that used in the tests of sensitivity. Strain T was used as the test organism; the inoculum was 10^{-4} cc. containing 50,000–100,000 organisms, and 2-fold dilutions of the urine and plasma were made in broth.

Treatment. Almost all of the streptomycin was given intramuscularly. The total daily dose was 2.5 to 6 Gm. given in 0.5 to 1.0 Gm. amounts every four to six hours. The numbers of patients receiving the different daily doses were as follows:

Gm. per Day	No. of Cases
2.5	1
2–3	2
3.6	1
4.0	9
4.8	3
5.4	2
6.0	3

An initial intravenous dose of 0.5 to 1.0 Gm. of streptomycin was given to nineteen of the patients immediately before the first intramuscular injection. The intravenous doses were given in a volume of 20 ml. and the intramuscular doses in 4 or 5 ml. of physiological sodium chloride solution. The streptomycin treatment was usually continued for about seven days unless an untoward reaction prompted its discontinuance. One patient, whose urine contained *Streptococcus viridans* as well as a gram-negative organism, was given intramuscular penicillin 320,000 units daily along with the streptomycin.

The urine was alkalinized before and during treatment in fourteen cases. This was done by the oral administration of sodium bicarbonate

* These studies were carried out, in large part, in the bacteriological laboratory of the Mallory Institute of Pathology with the help and guidance of Miss Marion E. Lamb and Dr. Robert N. Nye who were also helpful in the classification of the organisms.

† These determinations and the streptomycin levels were done by Clare Wilcox.

and potassium citrate, the usual dose being 1 Gm. of each six times daily. Slightly higher doses were necessary in four cases in order to keep the urine alkaline. Two patients received only sodium bicarbonate. Generally, the patients were kept on the alkali therapy for a control period of at least two days before streptomycin was begun, in order that the effect on the urinary flora could be ascertained. However, only one case included in this study showed a significant reduction in the bacilluria by alkalinization alone.* In seven patients, six of whom are included in a previous report[7] no attempt was made to alter the urinary pH.

CASE REPORTS

The patients in the first six cases were treated with streptomycin without adjuvant alkali administration. The pyuria and bacilluria were unaffected and *in vitro* tests showed that the failures were associated with the rapid development of streptomycin resistance by the infecting organisms. These six cases are reported in detail elsewhere.[7] The urine was acid before and throughout the course of therapy in five of these six patients.† In Case 6, the specimens of urine obtained immediately before streptomycin treatment was started were alkaline. Only *B. proteus* could be isolated from cultures of these specimens and from the ones obtained during the first two days of therapy although the urine became acid immediately after the streptomycin was started and remained acid throughout the period of observation. No organisms could be grown from the cultures of the urine obtained on the third and fourth day of treatment in this case but pyuria and bacilluria recurred on the fifth day of therapy. The organism recovered on that day and thereafter was a strain of *E. coli* that was totally resistant to streptomycin. Earlier cultures in this case were reported as showing both *B. proteus* and *E. coli* but the latter organism could not be isolated from cultures obtained during the three-day control period just prior to the streptomycin administration.

In only one patient treated without alkalis did the urinary tract infection respond favorably to streptomycin.

CASE 7. The significant data in this case are shown in Figure 1. The patient had rheumatic heart disease and had many hospital admissions for attacks of congestive cardiac failure, pulmonary emboli and paroxysmal tachycardia. Since 1940 she also had marked but symptomless pyuria which failed to respond to the usual therapies, including several courses of sulfonamides. In May, 1946, she was admitted because of severe dyspnea, some edema and moderate precordial pain. At that time left costovertebral angle tenderness was elicited but there was no suprapubic discomfort. Repeated urine examinations showed gross pyuria, 3+ albumin, and numerous gram-negative bacilli. Cultures of the urine all showed *Escherichia coli*. The cardiac symptoms responded promptly to rest and digitalis. On the sixth day in the hospital she was started on streptomycin. Alkalis were not given but the ammonium chloride which she had been receiving was discontinued during the streptomycin therapy. The blood nonprotein nitrogen was 34 before and 25 mg. per 100 cc. after this therapy. Although the urine remained markedly acid, the coli bacilluria and the pyuria cleared rapidly and did not recur during a four-month follow-up except for a few leukocytes seen in the sediment on one occasion.

There were five patients (Cases 8–12) from whose urine a single organism was cultured and who responded favorably to streptomycin and alkali therapy. The infecting organism was *Aerobacter aerogenes* in three of them and *Escherichia coli* in the other two. Except on two occasions shortly after the end of treatment in Case 10, the urine remained sterile in every instance during the therapy and over a follow-up period varying from seven weeks to five and one-half months. The pyuria cleared completely in three of these cases and was markedly diminished but persisted in the other two so that only a few pus cells were seen on microscopic examination of the spun sediment of urine collected after the first two or three days of streptomycin. The relevant information concerning these cases is

* There were two patients, however, in whom the infection cleared during the control period when alkalis were given alone. Streptomycin was not used in these cases and they are not included in this report.

† In the present report the cases are numbered consecutively and Nos 1–6 correspond to those previously reported.[7]

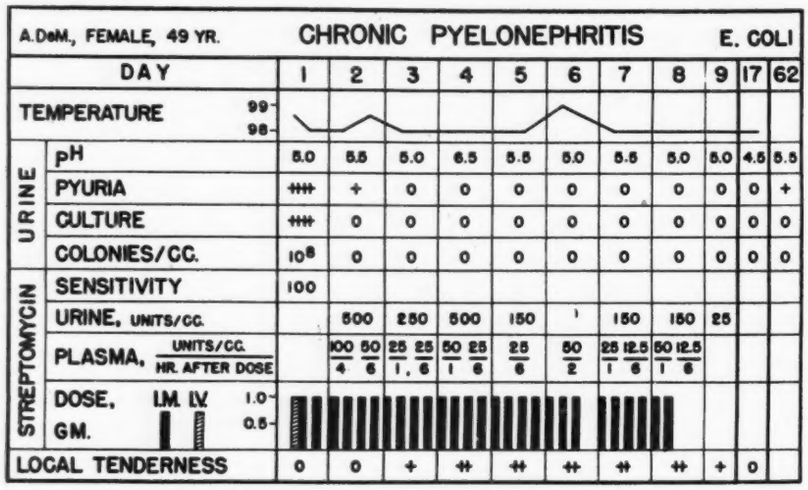

FIG. 1. Case 7. Alkalis were withheld in this case because of congestive heart failure. The streptomycin treatment was successful although the urine remained acid throughout.

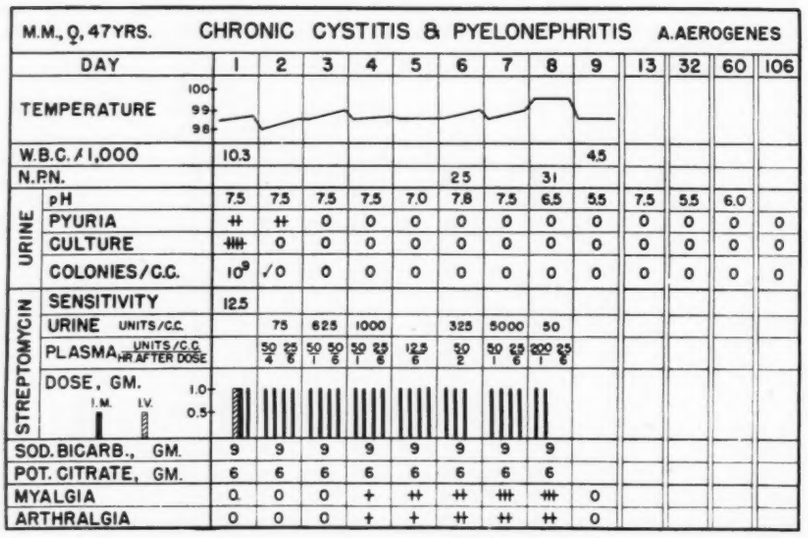

FIG. 2. Case 8. The patient entered the hospital in diabetic coma from which she recovered on appropriate treatment. In the meantime, she developed cystitis and pyelonephritis presumably through a catheter which had been kept in place for several days. Three separate courses of sulfadiazine and one of sulfathiazole failed to control the pyuria and the bacilluria. The infection had been present for three months when therapy with alkalis and streptomycin was begun. At that time the patient was convalescing from acute infectious hepatitis of about a month's duration. The urinary infection responded promptly and the urine has remained sterile and free of pus during a three months' follow-up. Albumin was found in the urine before but not after the treatment. Renal function was normal throughout and liver function improved steadily. Arthralgia and myalgia occurred and increased in severity during the latter part of the therapy and fever appeared on the last day, but all these manifestations cleared promptly after streptomycin was stopped.

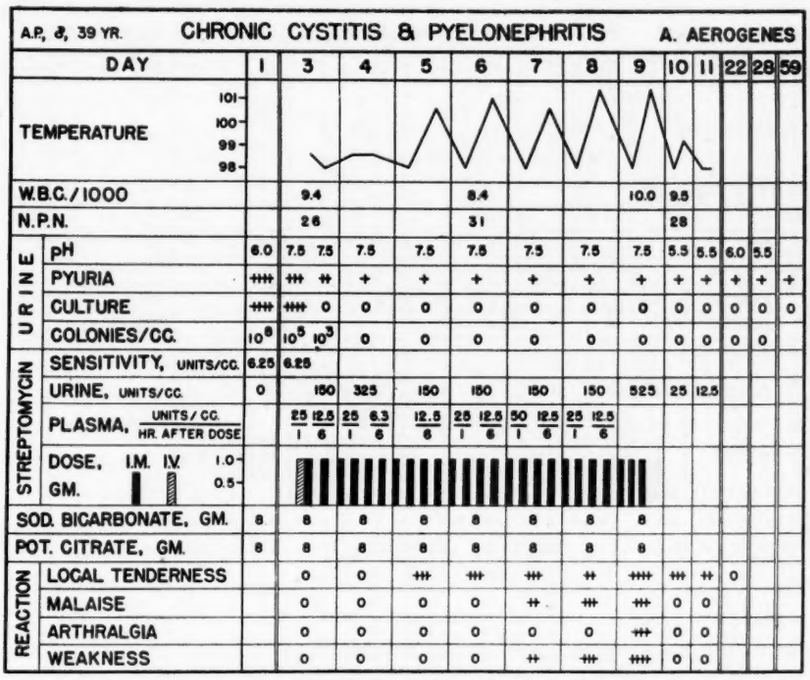

FIG. 3. Case 9. This patient underwent a surgical resection of the rectum for carcinoma and developed cystitis and pyelonephritis from an indwelling catheter. During three months of persistent infection, separate courses of sulfadiazine, sulfathiazole and penicillin were given without effect. Urinary alkalinization and streptomycin treatment resulted in rapid clearing of the bacilluria but a few pus cells were seen in the sediment of the later specimens. There was no alteration in renal function in this case. The patient has had no symptoms and urine cultures have remained sterile during a follow-up period of seven weeks. Fever, malaise and arthralgia cleared promptly after the streptomycin was discontinued but the gluteal tenderness subsided more slowly.

given in Figures 2–6 and in the legends which accompany these figures.

There were three other cases (Cases 13–15) in which a single organism was isolated before treatment but only temporary improvement was obtained by therapy. In each instance an organism was isolated after treatment which was different from the one found during the control period before streptomycin was started. In one case an organism resembling the original strain also appeared at a later date. With one exception the new strains isolated after treatment were sensitive to streptomycin.

The findings in Case 13 are shown in Figure 7. The late recurrence of pyuria and bacilluria during the sixth week after the treatment was stopped was considered to be a reinfection in this case. The significance of the dizziness and instability that were noted after the therapy was difficult to evaluate in view of the previous history of the patient.

In Case 14, there was only slight and temporary improvement but a streptomycin resistant strain of *Aerobacter aerogenes* replaced the original sensitive strain of *E. coli* in the urine. The possibility that the Aerobacter was present but undetected in the urine before treatment cannot be ruled out. The findings are shown in Figure 8.

In Case 15 (Fig. 9) there was temporary improvement with a recurrence of infection, first with a new strain not previously isolated and later with an organism similar to the original strain in every respect including its sensitivity to streptomycin. The new strain also was sensitive to the antibiotic.

The next three cases (Cases 16–18) are of interest because in each instance the urine was

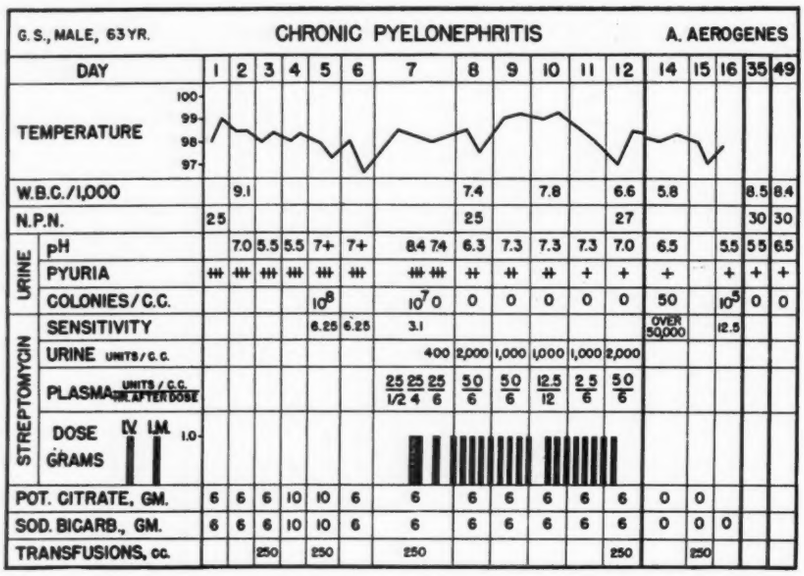

FIG. 4. Case 10. The urinary tract infection followed suprapubic removal of a papillary carcinoma of the bladder. Cystoscopy revealed no recurrence of the tumor but retrograde pyelograms showed dilation of the right ureter and renal pelvis. There was no diminution of renal function. A course of sulfadiazine had been unsuccessful and pyuria and bacilluria with *Aerobacter aerogenes* had been present for ten weeks before urinary alkalinization and streptomycin therapy was begun. Cultures were negative during treatment, but *A. aerogenes*, which grew in the presence of 50,000 units of streptomycin per cubic milliliter, was obtained on the second day after the treatment was ended. Two days later, at the time of discharge from the hospital, a streptomycin sensitive strain of the same organism was recovered. Except for these two occasions the urine was sterile and remained so during a follow-up period of five and one-half months. Microscopic pyuria, however, has persisted. No other treatment was used for the urinary infection. Local tenderness at the sites of the injection was the only untoward effect of the streptomycin.

infected with two organisms and the infection responded to alkalinization and streptomycin. Two of these cases had renal calculi and in the third the urinary infection was secondary to an acute prostatitis.

CASE 16. This was the patient's sixth hospital admission. In 1943, he had hematuria and lumbar pain for two months and was then found to have bilateral staghorn calculi. A right pyelolithotomy was performed in July of that year and a left nephrectomy, three months later. In November, 1943, the patient developed acute pyelonephritis, was treated with sulfathiazole and made an uneventful recovery. In March, 1945, he had a second attack of acute pyelonephritis. At this time *B. proteus* and Friedländer's bacillus were obtained from cultures of the urine. Sulfadiazine therapy was begun but had to be discontinued because of high drug levels in the blood. Methenamine therapy was instituted and the patient became symptom free but the pyuria persisted. In February, 1946, he had a third attack of pyelonephritis. Treatment with sulfadiazine, penicillin and methenamine was followed by symptomatic improvement but the pyuria and bacilluria were unaffected. An intravenous pyelogram then revealed two small stones in the right kidney.

The patient was admitted for streptomycin therapy on May 6, 1946. He was then symptom free and afebrile. His blood pressure was 150/100. Mild tenderness was elicited in the right upper quadrant of the abdomen. Routine hematological findings were normal. The urine was cloudy, malodorous, showed 2+ albumin and the centrifuged sediment contained in-

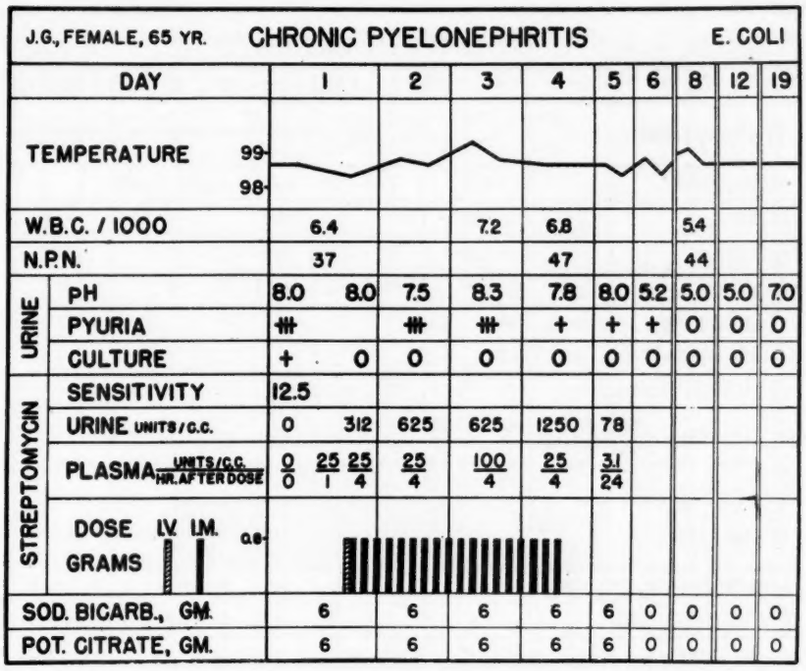

FIG. 5. Case 11. This patient was admitted for acute gastroenteritis, but was found to have persistent pyuria and bacilluria, and *E. coli* was cultured from the urine. Culture of the urine became negative promptly after alkali and streptomycin therapy was started. The urine became grossly clear on the third day and the sediment was free of pus cells within a week. Treatment was concluded on the fourth day because of moderate vertigo which began on the second day but this disappeared one day after the streptomycin was stopped. Many subsequent urine cultures have been sterile and only an occasional pus cell has been found in the spun sediment of some of the specimens obtained during a three months' follow-up.

numerable pus cells and bacilli and a few red blood cells and fine granular casts. Cultures of the urine all yielded an "atypical" Friedländer's bacillus and *B. proteus*. There was poor excretion of dye and the maximum concentration of the urine was low. Chloride, calcium, phosphorus and phosphatase determinations in the blood were normal. Therapy with sodium bicarbonate was begun eight days after admission and streptomycin was started three days later. The relevant findings thereafter are shown in Figure 10. The first urine culture obtained seventeen hours after the initial dose was sterile. Numerous additional cultures made during treatment and during the three-month follow-up period were all sterile. Pyuria, however, was only temporarily reduced during the last three days of treatment. The blood nonprotein nitrogen was somewhat elevated but was unaffected by the treatment.

Local tenderness developed in the injection sites on the third day and increased progressively with each injection. On the ninth and tenth days the gluteal regions showed large areas of redness, heat and induration. At this time a reddish maculopapular rash appeared on the extensor surfaces of both thighs and on the back. After the second day of treatment, the patient complained of mild dizziness while walking but the neurological examination was negative. Streptomycin was continued and the vertigo cleared for three days and then reappeared along with some headache on the eighth day. These symptoms increased during the next two days and on the tenth day there was marked headache, tinnitus and vertigo, the latter occurring with any motion of the head. The patient was unable to walk because of unsteadiness. Treatment was then omitted. The symptoms disappeared within six hours and the

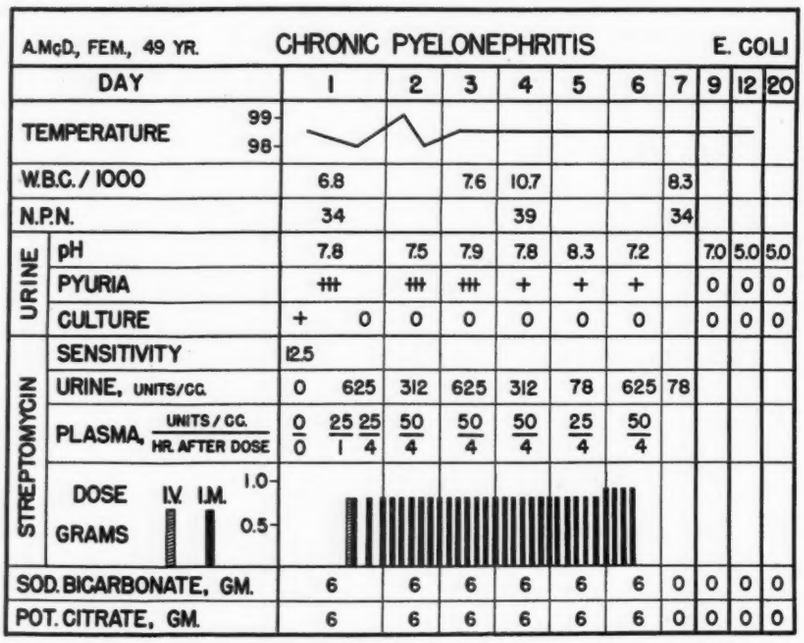

FIG. 6. Case 12. The patient had hypertension (blood pressure 240/130) and slightly diminished renal function (dye excretion and concentration of the urine) but no urinary tract symptoms except nocturia. She was admitted to the hospital because of urticaria which followed medication with penicillin and other drugs that were given at another hospital for an acute gastrointestinal upset. The urticaria and symptoms cleared promptly but she was found to have persistent pyuria and bacilluria without albuminuria. After alkalinization of the urine, streptomycin was given. The urine promptly became sterile and remained so for a follow-up period of two months. The urine remained cloudy for two days, then showed only a few pus cells in the sediment for three more days and finally cleared completely and has remained clear. There were no untoward reactions during the treatment, but eight days after it ended the patient developed ataxia. Caloric and rotation tests showed reduced labyrinthine function but there was no vertigo, tinnitus or nystagmus. The ataxia improved within a month and the patient walked normally after two months.

patient remained symptom-free for five days. Severe vertigo and mild tinnitus then recurred. A neurological consultant found no neurological changes other than marked subjective discomfort on sudden motion of the head and unsteadiness of gait and considered this to be an acute labyrinthine disturbance. Caloric and irrigation tests were negative and audiograms were essentially normal. Five days after the second attack of vertigo began, the patient became ambulatory but his gait continued to be unsteady. One month later he observed motion of distant objects in the lateral fields of vision and examination revealed slight but sustained nystagmus on extreme left lateral gaze. The nystagmus and vertigo gradually subsided during the next month, but the unsteady gait persisted.

CASE 17. This patient had had three attacks of acute left pyelonephritis at three-month intervals before January, 1946, when he was found to have bilateral renal calculi. A right pyelolithotomy was performed at that time and he was given sulfadiazine, 4 Gm. daily for two months but the pyuria persisted. In June, 1946, he was treated with methenamine. Again his symptoms improved but the pyuria was unaffected. His blood pressure and renal function tests were normal. Retrograde pyelograms showed calculi in the pelvis of the left kidney. Cultures of the urine from the right ureter grew Friedländer's bacillus and those from the left

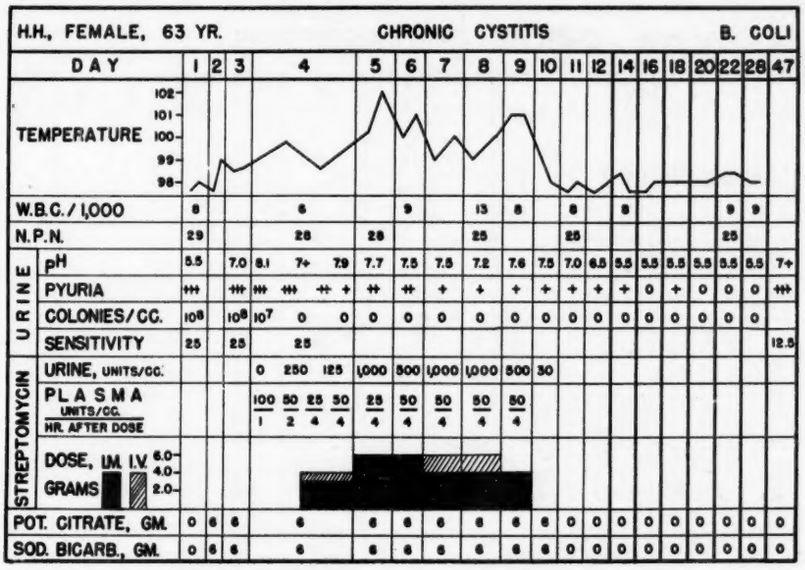

FIG. 7. Case 13. This patient had recurrent attacks of cystitis for many years, and weakness, dizziness and anorexia for four months. Marked pyuria and bacilluria were demonstrated during the ten days prior to streptomycin treatment. The blood pressure was 180/100 but the renal function was normal. The urine was rapidly sterilized after alkalinization and streptomycin administration and remained free of bacteria until the patient was discharged nineteen days later. During the sixth week after the treatment ended, the urinary infection recurred. The organism at this time, however, was a strain of *B. coli communis*, sensitive to 12.5 units, whereas the organism isolated on two occasions before treatment was *B. acidi lactici*, sensitive to 25 units of streptomycin. As the patient became ambulatory, she complained of dizziness and had difficulty in walking for about five days, and the dizziness persisted in a minor degree throughout the follow-up period. There were no abnormal neurological findings.

yielded the same organism and also *B. fecalis alkaligenes*. Both of these organisms were found in numerous cultures of bladder urine.

Therapy with alkalis and streptomycin was started early in July. The relevant findings are shown in Figure 11. Cultures of urine obtained one and two hours after the first dose of streptomycin each showed a scant growth of Friedländer's bacillus. Those obtained thereafter, both during treatment and during a followup period of six weeks, were all sterile except for the appearance of *Pseudomonas aeruginosa*, probably as a contaminant, on one occasion. The pyuria decreased initially but recurred during the last three days of therapy and persisted thereafter.

CASE 18. A twenty-three-year old man entered the hospital twenty-four hours after the onset of chills, fever, nausea, vomiting and dysuria. On admission his temperature was 100°F. and pulse 100. There was tenderness in the suprapubic region, in both costovertebral angles and over the prostate. The urine was alkaline, contained a trace of albumin, and an occasional pus cell in the centrifuged sediment. Cultures yielded *Staphylococcus albus* and *Pseudomonas aeruginosa*. During six days of treatment with penicillin and sulfadiazine, the temperature returned to normal and the symptoms cleared but the pyuria persisted and urine cultures continued to be positive. At this time the prostate was enlarged and tender. The strain of *Ps. aeruginosa* isolated from the urine was sensitive to 25 units of streptomycin and the *Staphylococcus albus* was inhibited by 50 units. Treatment with sodium bicarbonate, 10 Gm. daily, was begun on the tenth hospital day. The pH of the urine was 7.5 on the twelfth day and streptomycin was then started. The initial dose was 1 Gm. intravenously and 1 Gm. intramuscularly and this was followed by 1 Gm. intramuscularly

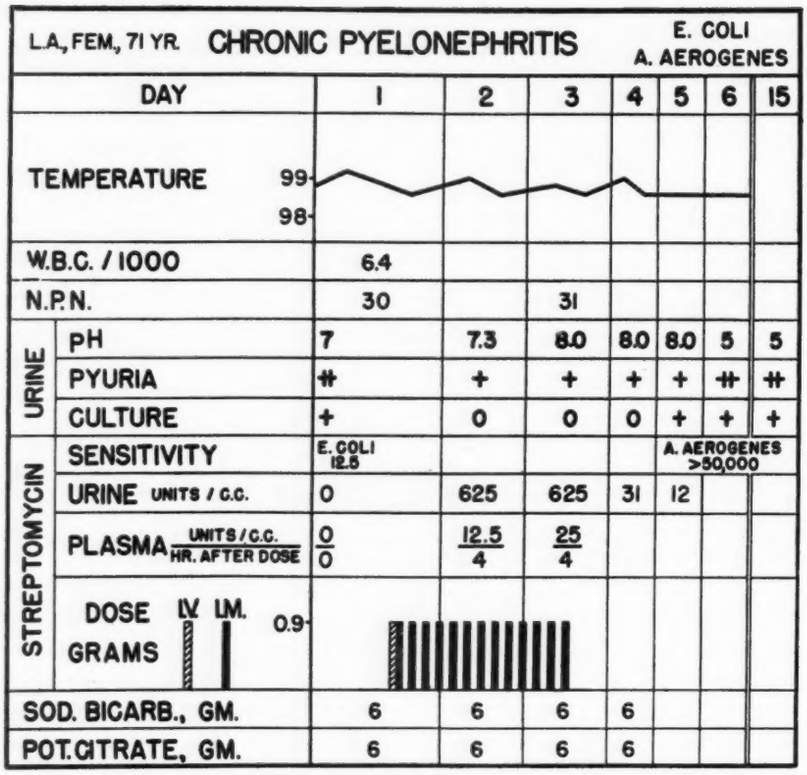

FIG. 8. Case 14. The patient was a mild diabetic who had had urgency, nocturia and occasional dysuria for one year and came to the hospital because of malaise, dysuria, frequency, fever and chills. With supportive therapy she quickly became asymptomatic but persistent pyuria was noted and *E. coli* was repeatedly cultured from the urine. The blood pressure was 180/96, there was a slight trace of albumin in the urine and the renal function was slightly diminished as judged by urine concentrations and dye excretion tests. Dizziness and some difficulty in walking were noted after forty-eight hours of therapy. The streptomycin was discontinued on that account and these symptoms subsided promptly. There was no tinnitus or nystagmus. Urine cultures were sterile during the first three days after institution of therapy, but on the fourth day and during a two-month follow-up period they all yielded a strain of *Aerobacter aerogenes* resistant to 50,000 units of streptomycin. The pyuria was diminished only temporarily.

every six hours for a total of 17 Gm. Tenderness at the injection sites was the only untoward reaction accompanying therapy. The pyuria and hematuria cleared and the urine cultures were sterile during treatment and thereafter. There has been no recurrence of symptoms, the urine has remained clear and cultures have been negative for three months.

The three remaining cases were all mixed infections which responded to treatment with alkalis and streptomycin by apparent temporary sterilization of the urine and by a reduction in the amount of pus. In each instance, however, the infection recurred, with the same organisms in Case 19 and with different strains in Cases 20 and 21. The strains that reappeared in Case 19 had the same sensitivity to streptomycin as did the original strains, while the new strains that appeared in the others were of varying sensitivity.

CASE 19. This patient was first admitted to the hospital in April, 1946, because of acute prostatitis and pyelonephritis. *E. coli* and *B. proteus* were cultured repeatedly from the urine and from prostatic secretions. He was started on a course of sulfadiazine, 4 Gm. daily and became symptom free but some pyuria persisted. After five days, however, he developed

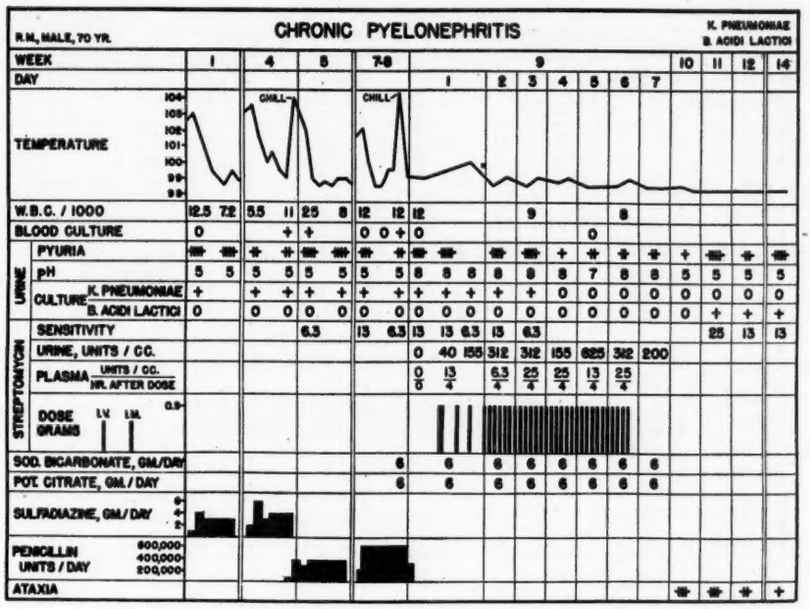

FIG. 9. Case 15. This patient had right renal lithiasis and recurrent attacks of acute pyelonephritis for two years. During two recent attacks, Friedländer's bacillus, type B, was repeatedly cultured from both blood and urine, and during the last episode, chills and fever persisted in spite of large doses of penicillin. The blood pressure was 150/80. There was some diminished renal function (ability to concentrate urine and excrete the test dye) and slight albuminuria. Urinary alkalinization and intramuscular streptomycin resulted in clinical improvement and sterile urine cultures were obtained both during treatment and for five days thereafter. The pyuria was only temporarily diminished. The blood non-protein nitrogen was 40 mg. per 100 cc. before treatment and 35 or less after the streptomycin was stopped. Twelve days after the treatment ended, the bacilluria recurred and only *B. acidi lactici* was grown in the cultures. Four weeks later, however, the Friedländer's bacillus, type B, was again found but not the *B. acidi lactici*. Both of the organisms obtained during the follow-up were sensitive to streptomycin, the Friedländer's bacillus being inhibited by 25 units like the strain isolated before the treatment. Some ataxia without tinnitus, dizziness or deafness was noted after the patient had been up for a few days. The ataxia improved gradually during the following month.

fever and a rash and the sulfadiazine was discontinued. He remained essentially asymptomatic until four days before the second admission in June, when he again developed acute pyelonephritis. This time he was given 1 Gm. of sulfathiazole and rapidly developed generalized myalgia, a maculopapular rash, chilliness and fever of 104.2°F. No more sulfonamide was given and symptoms and pyuria persisted for two weeks. *E. coli* and *B. proteus* were again found in the urine. There was slight intermittent albuminuria but the blood pressure and renal function were normal. Alkalis were started on the fifteenth hospital day and streptomycin was begun four days later.

The course and relevant findings are shown in Figure 12. Tenderness occurred at the site of every injection and increased progressively with the successive injections. On the fifth day of streptomycin treatment, there were large, very tender, indurated areas in both gluteal regions and the antibiotic was discontinued. During the last three days of the treatment the patient also complained of generalized muscular aches. Fever was present throughout the period of treatment and subsided promptly after the

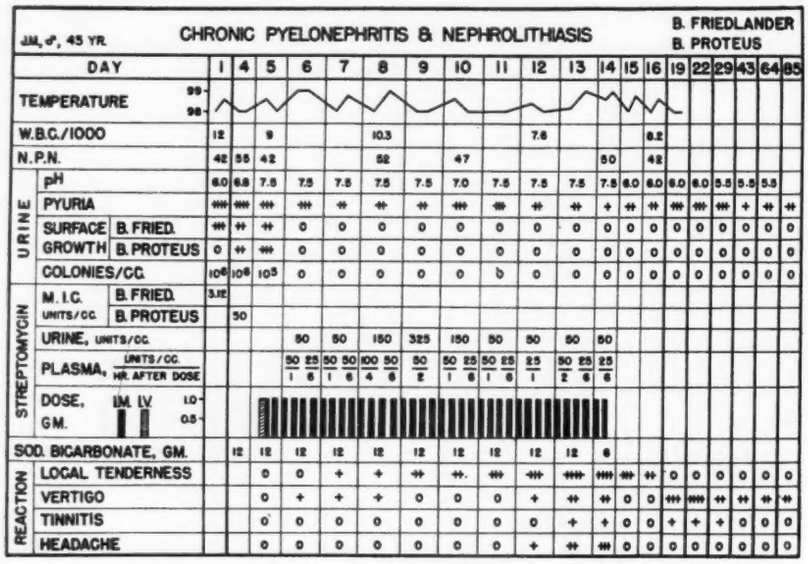

FIG. 10. Some of the relevant findings in Case 16.

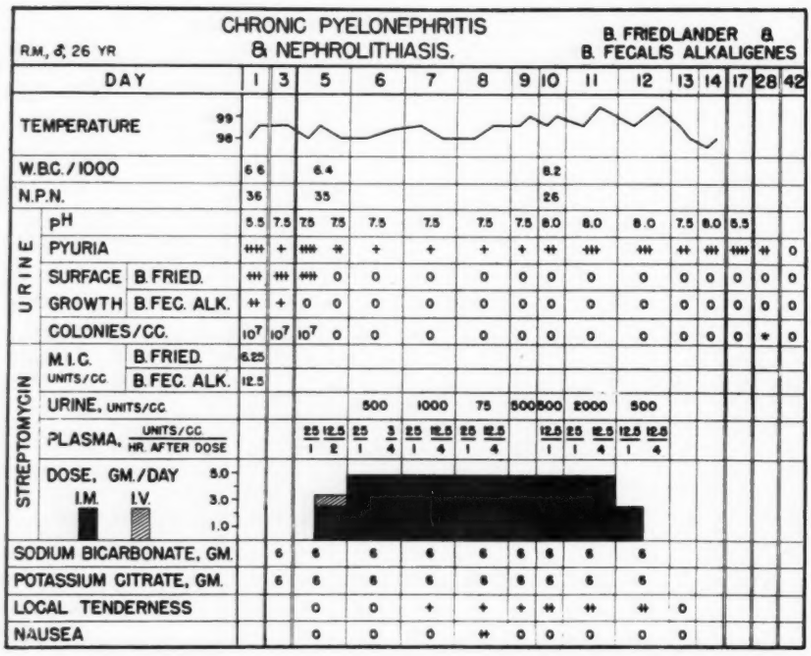

FIG. 11. Some data relevant to the streptomycin therapy in Case 17. *Pseudomonas aeruginosa* inhibited by 25 units of streptomycin isolated at this time only.

streptomycin was stopped. A culture of urine obtained one hour after the initial dose showed only a single colony of *E. coli* and one obtained after twelve hours was sterile. Pyuria cleared completely on the last day of therapy. The urine remained sterile throughout the streptomycin treatment and for a week longer. After that *E. coli* reappeared, and one week later, the urine was again purulent and contained both *E. coli* and *B. proteus*. Pyuria and bacilluria have persisted during the month since they reappeared. The organisms obtained before and after the streptomycin had the same sensitivity to the antibiotic.

CASE 20. Sixteen months before entry this patient developed acute prostatitis which was treated successfully with penicillin. During the next five months he had three attacks of acute

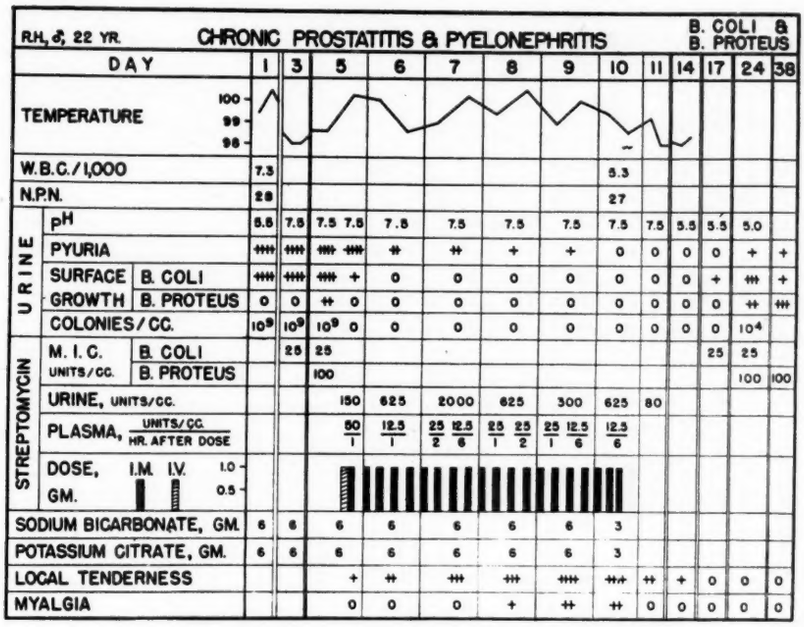

FIG. 12. Course and significant findings in Case 19.

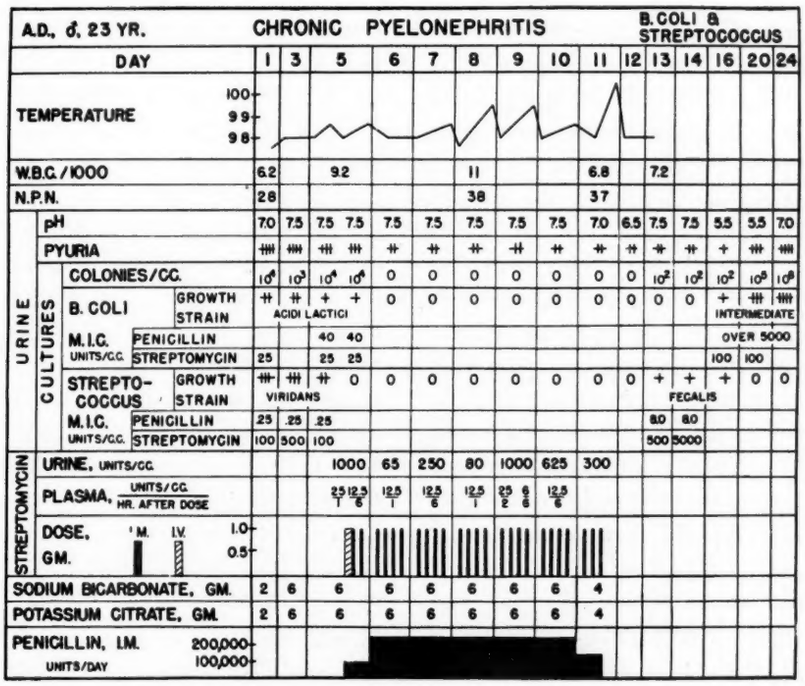

FIG. 13. Findings in Case 20.

pyelonephritis, the first one on the right, the others on both sides. The first and second attacks were treated successfully with sulfadiazine, but the development of neutropenia necessitated the omission of this drug during the third attack. Mandelic acid therapy was substituted and, although the symptoms regressed, pyuria and bacilluria continued for a period of eleven months until he was admitted to the hospital in June, 1946. Five pyelographic studies during this interval showed no obstructive lesions and only minimal dilatation of the minor calyces. The renal function was normal and the urine remained free of albumin, casts and red blood cells. The patient was given alkalis and five days later was started on streptomycin. Penicil-

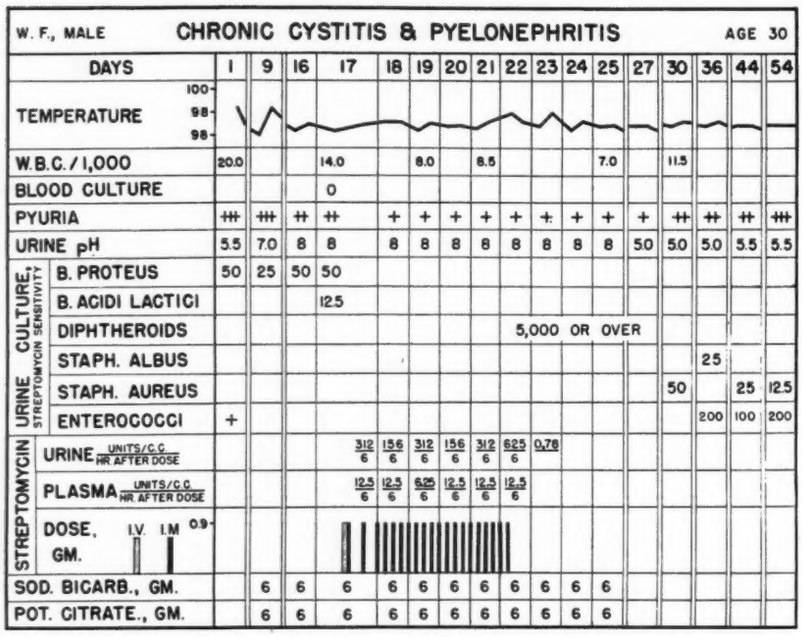

FIG. 14. Therapy and other significant findings in Case 21.

lin was given along with the streptomycin because the urine cultures showed both *Streptococcus viridans* and *E. coli* (acidi lactici type).

The therapy, course and other relevant data are shown in Figure 13. Tenderness and pain in the injection sites developed on the second day and persisted throughout the period of treatment and on the last day, there was also fever, headache, anorexia, malaise and generalized myalgia. These all disappeared within twenty-four hours after the streptomycin was discontinued. Urine cultures, one hour and six hours after the initial dose showed a scant growth of *B. coli*, but those obtained twenty-four hours later and throughout the period of therapy were sterile. The pyuria was considerably reduced throughout this period.

Two days after the streptomycin was discontinued an alpha hemolytic streptococcus appeared in the urine culture. This organism was different culturally from the one isolated before treatment and proved to be a strain of *Streptococcus fecalis*. It was also more resistant than the *Streptococcus viridans* to both streptomycin and penicillin. Three days later the urine culture yielded a coliform organism which was classified as the "intermediate type" of *E. coli* by its fermentation reactions. It was inhibited by 100 units of streptomycin but grew in the presence of 5,000 units of penicillin. Gross pyuria and microscopic bacilluria have persisted and repeated cultures have been positive for *E. coli* during a two-month follow-up period.

CASE 21. The patient was a healthy looking, thirty-year old man who, on the day after his birth was operated on for a meningocele associated with spina bifida. He never had bladder control and used a Cunningham penile clamp for ten years. He had numerous episodes of cystitis and pyelonephritis and cultures of the urine at various times in the past had shown *B. proteus*, alpha hemolytic streptococci and enterococci. The patient entered the hospital this time because of dysuria, frequency and costovertebral angle pain of two weeks' duration having received a course of sulfadiazine without benefit just before entry. Blood pressure and renal function were normal. Pyelograpy and cystography revealed a large bladder and a dilated urethra with a diverticulum containing a stone. The kidney pelves and ureters appeared normal.

In the hospital, *B. proteus* was isolated repeatedly from the urine over a two-week period and *E. coli* (acidi lactici type) was also obtained just before a course of therapy with alkalis and streptomycin was given. The effect of the treatment on the pyuria and on the bacteriological findings are shown in Figure 14. A specimen of urine obtained four hours after

the first dose of streptomycin was negative as were daily cultures thereafter until the streptomycin was stopped. After that various gram-positive organisms were obtained of which only the enterococci had also been demonstrated before therapy. The gram-negative bacilli did not reappear during a follow-up period of four and one-half weeks. There was subjective improvement with disappearance of costovertebral angle pain and tenderness. These did not return during the period of observation. The number of pus cells in the urine diminished temporarily while the treatment was being given. The stone in the diverticulum was removed transurethrally before the patient left the hospital.

TABLE I
RESULTS OF STREPTOMYCIN THERAPY IN RELATION TO ADJUVANT ALKALIS AND THE APPEARANCE OF RESISTANT STRAINS

Results of Treatment	Total Cases	Alkaline Urine	Acid Urine	Developed Resistance
Cured	9	8	1	1*
Transient improvement†	6	6†	0	1
Failure	6	0	6	6

* Patient received alkali. Resistant strain isolated only once after treatment and subsequent cultures were negative.

† One of these patients was free of infections for over five weeks and was considered as having a reinfection, since a different organism was found later.

RESPONSE TO TREATMENT

Sterilization of the urine was accomplished during streptomycin treatment in fifteen cases. In eight of them the urine was sterile within twelve hours after therapy began. The first negative cultures of the urine were obtained twelve to twenty-four hours after the initial dose had been administered to six patients, one patient showed persistence of bacilluria for forty-eight hours after therapy was instituted although there was a marked reduction in the number of bacteria found in the urine during this interval. Alkalis were used in the treatment of all but one of these fifteen cases.

Of the seven patients who received streptomycin without urinary alkalinization, five had persistent bacilluria throughout the period of therapy and only one of these five showed a significant reduction in the number of bacteria after therapy was instituted. In a sixth patient, cultures of the urine became sterile on the third day but there was a recurrence of bacilluria on the fifth day of treatment. Complete and lasting cure of bacilluria was accomplished in only one of these seven cases.

The pyuria was essentially unaffected in the patients from whom positive urine cultures were obtained throughout the period of treatment. In most of the other cases pyuria responded more slowly to therapy than did bacilluria. A significant reduction in the number of leukocytes in the urine occurred after one to four days of treatment in all of the fifteen cases whose urine cultures became negative. Complete disappearance of pus cells, however, occurred in only five of the cases. In two patients there was a reduction in the amount of pus in the urine during treatment but marked pyuria recurred after the streptomycin therapy was concluded, in spite of persistently negative cultures. Both of these patients had renal calculi. As would be expected, gross pyuria accompanied the relapses. Fever and symptoms referable to the urinary tract infection were quite mild in these cases and they responded irregularly to the therapy.

The results are summarized in Table 1. "Cures" in the sense of freedom from bacilluria persisting throughout the period of observation were achieved in nine cases. Alkalis were used in eight of these cured cases. In another patient who was treated with alkalis, sterile urine cultures were obtained throughout the period of therapy and for five and one-half weeks after the

streptomycin was stopped but the urine subsequently became reinfected with an organism which had not been isolated before the streptomycin was started. Transient improvement with freedom from bacilluria during the streptomycin administration and for less than two weeks thereafter was noted in five additional cases, all treated with alkalis.

vidual cases are shown in some detail in the accompanying figures. The findings are summarized for the cases treated without alkalis in Table II, and for those receiving adjuvant alkali therapy in Table III. In these tables are listed the organisms isolated before treatment, their sensitivity to streptomycin and also the relation of the streptomycin therapy to the appearance of resistant

TABLE II

BACTERIOLOGY OF THE URINE IN CASES TREATED WITH STREPTOMYCIN WITHOUT ALKALIS

Case	Isolated Before Treatment		Result of Therapy	Isolated During Streptomycin Therapy			
	Organism	M.I.C.		Organism	M.I.C.	Previous Treatment	
						Gm.	Days
1	Paracolon bacillus	25	Failure	Paracolon bacillus	over 50,000	6	4
2	Friedländer's bacillus	12.5	Failure	Friedländer's bacillus	over 50,000	3.25	2
3	Aerobacter aerogenes	12.5	Failure	Aerobacter aerogenes	over 50,000	3	1
4	Escherichia coli	50	Failure	Escherichia coli	over 50,000	8	1
5	Friedländer's bacillus	6.3	Failure	Friedländer's bacillus	over 50,000	7	1
	Pseudomonas aeruginosa	12.5		Pseudomonas aeruginosa	over 50,000	19	3
6	Bacillus proteus	100	Failure	Escherichia coli	over 50,000	12.5	4
7	Escherichia coli	100	Cured				

M.I.C. = minimum inhibiting concentration in units (micrograms) of streptomycin per ml.

In the remaining six cases the bacilluria was essentially unaffected. Alkalis were not used in any of these cases and the urine remained acid throughout the streptomycin treatment. Resistant strains were isolated from all of these six patients during the streptomycin treatment. Resistant strains were also isolated from two of those who were treated with adjuvant alkalis. In one of the latter the resistant organism was isolated only once during the follow-up studies and this was not accompanied by other evidence of reinfection. In the other case the resistant strain first appeared two days after therapy ended and it is not certain whether the new strain was present but undetected before treatment or whether this was a reinfection with a new strain.

The bacteriological results in the individual cases are shown in some detail in the accompanying figures. The findings are summarized for the cases treated without alkalis in Table II, and for those receiving adjuvant alkali therapy in Table III. In these tables are listed the organisms isolated before treatment, their sensitivity to streptomycin and also the relation of the streptomycin therapy to the appearance of resistant strains corresponding to those present before treatment was started. The occurrence and streptomycin sensitivity of new strains during or after streptomycin treatment are also indicated.

Sensitivity of Strains Before Treatment. The Friedländer's bacilli and some of the strains of *Aerobacter aerogenes* were the most susceptible of the organisms isolated before treatment. They were inhibited by about 3–6 units per ml. The strains of *B. proteus* and two of the strains of *E. coli* were the most resistant of the gram-negative organisms and required 50–100 units. The remaining gram-negative bacilli including the two strains of *Pseudomonas aeruginosa* were intermediate in sensitivity and required 12.5–25 units per ml. for complete inhibition. Other and more extensive reports indicate that

TABLE III

BACTERIOLOGY OF URINE IN CASES TREATED WITH STREPTOMYCIN AND ALKALIS

Case	Isolated Before Treatment		Streptomycin Therapy			First Negative Urine Culture (Hr. after First Dose)	Isolated after Streptomycin Treatment		
	Organism	M.I.C.†	Days	Gm.	Result		Organism	M.I.C.†	Days after Therapy Ended
8	Aerobacter aerogenes	12.5	7	28	Cured	18			
9	Aerobacter aerogenes	6.3	6	26	Cured	18			
10	Aerobacter aerogenes	3.1–6.3	5	20	Cured*	4	Aerobacter aerogenes	over 50,000	2
							Aerobacter aerogenes	12.5	4*
11	Escherichia coli	12.5	3	15.2	Cured	4			
12	Escherichia coli	12.5	5½	25.2	Cured	4			
13	Bacillus acidi lactici	25	5½	32	Reinfection	4	Escherichia coli communis	12.5	38
14	Escherichia coli	12.5	2	12.6	Temporary improvement	12	Aerobacter aerogenes	over 50,000	2
15	Friedländer's bacillus	6.3–12.5	5	29.7	Temporary improvement	72	Bacillus acidi lactici	12.5–25	12
							Friedländer's bacillus	12.5	34
16	Friedländer's bacillus	3.1	9	37	Cured	17			
	Bacillus proteus	50							
17	Friedländer's bacillus	6.3	7	34.4	Cured	4			
	Bacillus fecalis alkaligenes	12.5							
18	Pseudomonas aeruginosa	25	5	17	Cured	24			
	Staphylococcus albus	50							
19	Escherichia coli	25	5	21	Temporary improvement	12	Escherichia coli	25	7
	Bacillus proteus	100					Bacillus proteus	100	14
20	Bacillus acidi lactici	25	6	26	Temporary improvement	24	Escherichia coli (intermediate)	100	5
	Streptococcus viridans	100–500					Streptococcus fecalis	500–5000	3
21	Bacillus proteus	25–50	5	18.9	Temporary improvement	4	Diphtheroids	5000 or over	1
	Bacillus acidi lactici	12.5					Staphylococcus aureus	12.5–50	8
	Streptococcus fecalis						Streptococcus fecalis	100–200	14
							Staphylococcus albus	25	14

* Cultures were negative during further five and one half-month follow-up.
† Minimum inhibiting concentration in units (micrograms) of streptomycin per ml.

strains of the latter organism are often relatively resistant to streptomycin.[12,13]

Occurrence of Resistant Strains. Extreme resistance, that is, the ability to grow well in 50,000 units of streptomycin per ml., was demonstrated in nine strains isolated during or after the streptomycin treatment. Seven of these strains were identical in their morphological and cultural characteristics and in their biochemical reactions with the corresponding streptomycin-sensitive strains isolated before streptomycin treatment was started. Of the two other resistant organisms one was a strain of *A. aerogenes* obtained in Case 14 on the second day after treatment was stopped. The only organism identified in cultures of the urine of this case before the streptomycin treatment was a strain of *E. coli* that was inhibited by 12.5 units. In Case 6, a resistant strain of *E. coli* was found on and after the fifth day of streptomycin treatment. On several occasions prior to the beginning of therapy in this case cultures were reported as yielding *B. proteus* and *E. coli*. The latter organism, however, was not found in the control cultures made during the three days preceding the streptomycin therapy and the earlier cultures were not available so that their sensitivity and cultural characteristics could not be compared with the post-treatment strains. In this small group of cases there seemed to be no correlation between the degree of sensitivity of the strains isolated before treatment and the development or appearance of resistant strains during or after streptomycin therapy.

Mixed Infections. A single organism was isolated and identified in fourteen cases and two distinct bacterial strains were recovered in seven cases before the streptomycin treatment was started. Alkalis were given to eight of the patients with a single strain and to six of those with mixed infections.

Among the eight with a single strain, essential cures of the infection were achieved in five cases, there was a reinfection in one and early relapse in the other two. Among the six patients who were treated with alkali and had mixed infections three were cured and the other three showed only temporary improvement followed by a relapse of infection with the same or with other organisms. This small number of cases tends to confirm the observation[6] that, in general, streptomycin treatment is less successful in patients with infections caused by a mixed flora than in those with a single susceptible organism.

Appearance of New Strains. New strains, distinct from those isolated from the urine before treatment, were identified in cultures obtained from five patients after the treatment with streptomycin and alkalis was ended. Some of the new strains were gram-positive bacteria having varying degrees of sensitivity to streptomycin. There were also four strains of gram-negative bacilli, one from each of four patients and only one of them (the *A. aerogenes* in Case 14) was totally resistant. The other new strains of gram-negative bacilli which appeared after the conclusion of treatment were similar in sensitivity to the pretreatment strains of similar organisms isolated from other patients.

Streptomycin Levels. Plasma and urine levels of streptomycin are given in the charts of the individual cases. They tended to vary in general with the dose of streptomycin and with the interval between injections. In most of the cases the plasma levels found throughout the treatment period and even on the first day of treatment were equal to or higher than the original *in vitro* sensitivity of the infecting organism. A progressive increase in the plasma level during the course of therapy was demonstrated in only three instances, in two patients who received one Gm. every four hours (Cases 4 and 5) and in one who was given 1 Gm. every six hours. (Case 3.) The renal function was slightly reduced in Cases 4 and 5 but was normal in Case 3. In no instance, however, was the cumulative increase striking. Buggs and his co-workers[14] obtained a cumulative effect only in critically ill patients or in those with diminished renal function.

The levels of streptomycin found in individual specimens of urine collected daily showed marked variations ranging between 25 and 2,000 units per ml. No attempt was made to determine the total amount of streptomycin excreted or to follow the rate of excretion after single doses. Reports of such studies indicate that 50–70 per cent of the parenteral dose can be recovered from the urine.[14–17]

UNTOWARD REACTIONS

Four types of untoward reactions were encountered. The most frequent, although not the most serious, was pain and tenderness at the sites of injection. This was noted in almost every case, was usually mild, began during the latter part of the course of treatment and disappeared within one day after the injections were discontinued. Pain and tenderness severe enough to interfere with ambulation was experienced by seven patients. Three others developed severe pain, heat, redness and induration of the gluteal areas, which persisted for two to six days after the conclusion of therapy. This reaction prompted the premature interruption of therapy in two of them and necessitated a change to intravenous administration in the third.

Fever, probably attributable to the streptomycin developed in ten cases and occurred at various times after the beginning of treatment. It was first noted on the eighth day in one case but usually began during the second or third day. Four additional patients had fever during treatment which may have been caused by the infection.

Anorexia, malaise, headache, weakness, myalgia and arthralgia were among the symptoms experienced by five of those with fever. These symptoms usually disappeared within twelve hours after therapy was concluded.

A "histamine-like" reaction consisting of flushing and headache was experienced by three patients during intravenous injections that were probably given too rapidly. Transient syncope and clonic seizures accompanied this reaction in one patient. These were subsequently avoided by giving the intravenous streptomycin more slowly and in more dilute solution.

The most serious reaction was an acute labyrinthine disturbance which developed in one case after ten days of therapy. Nystagmus persisted for one week but vertigo on sudden motion of the head and unsteady gait have persisted with decreasing severity in this case for three months. Because of abnormal renal function and mild azotemia, this patient was given only sodium bicarbonate as an alkalinizing agent, potassium compounds being withheld because of the danger of retention and consequently disturbances of cardiac conduction. The possibility of a disturbed electrolytic balance inciting Ménière's disease must be entertained.

Two other patients developed mild vertigo which began forty-eight hours after the streptomycin was started and occurred only when they stood up. Therapy was immediately discontinued and the symptoms subsided within twelve hours. Three elderly patients who had hypertension and arteriosclerosis developed vertigo after the treatment was concluded, but the relation of the streptomycin therapy to their symptoms is dubious.

There were six patients who showed increases of the blood nonprotein nitrogen values during treatment. In only one patient who was quite dehydrated during the period of treatment was this rise appreciable. The urine of four patients revealed a few granular casts during streptomycin administration, but this may have been due to concomitant fever and dehydration.

Untoward reactions similar to those observed in this series have been reported by others.[8,16,18–20] Brown[20] encountered twenty-three cases of labyrinthine disturbance among patients receiving prolonged treatment with streptomycin and Molitor observed similar disturbances of gait and posture in dogs.[21]

COMMENTS

Although streptomycin has a marked antibacterial effect *in vitro* on most of the gram-negative bacilli which are important in infections of the urinary tract,[1,12,13,22] the results of therapy of such infections have not been uniformly favorable.[1,5–9] In the 409 cases collected by the Committee on Chemotherapeutics and Other Agents of the National Research Council[6] the over-all recovery rate was only 42 per cent. A similar recovery rate was obtained in the present small series.

Most of the possible causes for the failures have been outlined by Reimann, Price and Elias.[1] Among them the rapid development of streptomycin-fastness by the infecting organism is one of the most important.[7–10,14] There are numerous reports which demonstrate the relative ease with which various organisms can be made to acquire streptomycin resistance *in vitro*[23–31] and Knop[11] has produced fastness rapidly in thirteen strains from urinary tract infections by using urine containing various concentrations of streptomycin as the culture medium.

The findings in the first six cases illustrate very strikingly the significance of this factor in the treatment of urinary tract infections with streptomycin. In these cases resistant strains, indistinguishable culturally and biochemically from the pretreatment sensitive

strains, were obtained after from one to four days of treatment.

That dosage alone was not the primary factor in these cases is indicated by the fact that increases in dosage to almost the maximum tolerated amounts did not prevent the appearance of resistant strains.[7] Attempts were made to produce similar degrees of resistance in some of the pretreatment strains from these cases by cultivation in streptomycin containing media. From thirteen to forty-nine daily transfers on solid media were required. During these studies, isolated colonies were occasionally observed to grow well in the early transfers in concentrations of streptomycin which, though low, were adequate to inhibit the remainder of the inoculum and no growth was observed on the plates containing some lower concentrations of the antibiotic. Such colonies, after preliminary subculture in streptomycin-free media, were found to be totally resistant. These *in vitro* studies, which are reported in detail elsewhere,[31] suggest that resistance may be acquired by the same strain either by gradual adaptation or by sudden appearance of resistant forms. The *in vitro* studies suggest that the latter ones are mutants having the new characteristics. In the patient, however, it is not possible to say whether the same is true or whether the resistant form was originally present and was merely selected after elimination of the sensitive cells through exposure to streptomycin.

Streptomycin activity is much greater *in vitro* in an alkaline than in an acid medium.[32–34] Abraham and Duthie,[34] tested the activity of streptomycin against *Strep. pyogenes*, *Strep. fecalis*, *Staph. aureus*, *B. proteus*, *Bact. coli*, *Bact. typhosum* and *Ps. pyocyanea* using both large and small inocula. They found that an increase in the pH of the media from 6 to 8 increased the activity of streptomycin by 2 to 67-fold. A suggestion of the possible influence of this factor *in vivo* was obtained in Case 6. The urine was alkaline before treatment in this case owing to a *B. proteus* infection. When streptomycin was started, that organism was rapidly suppressed and then completely eliminated although it was not highly sensitive. The urine then became acid and a resistant *E. coli* appeared. In view of this observation and the more convincing *in vitro* evidence, an attempt was made to determine whether alkalinization of the urine during streptomycin therapy would increase the efficiency of treatment and reduce or prevent the development of resistance.

The results, as summarized in Table 1, suggest that alkalinization did, indeed, have a very favorable influence. Of fourteen patients in whom the urine was kept alkaline throughout the period of streptomycin therapy, eight were apparently cured of their infection. Cultures of urine obtained a few hours after the first dose of streptomycin were sterile and the urine has remained bacteria-free during the follow-up period. In the remaining six cases, the infection of the urine cleared during the treatment and for varying periods thereafter. The organisms that were found after the treatment in most of these cases were different from the pretreatment strains and, for the most part, were as sensitive to streptomycin as similar strains that have not been exposed to the antibiotic.

The source of the new strains which appeared after the course of alkalis and streptomycin is not clear. They may have been present and could not be isolated from pretreatment urine specimens by the methods used. If this were true, the findings would suggest that alkalinization not only enhanced the action of the streptomycin but also prevented the development of resistant strains in most cases. This possibility cannot be dismissed since some of the strains isolated after treatment with alkalis and streptomycin were similar, both culturally

and in their sensitivity, to the corresponding pretreatment strains.

It is to be borne in mind that the present treatment was directed against the infections and not against the underlying defects which made these infections possible or which contributed to their persistence. The organisms concerned are similar to those normally found in the bowel and sources of reinfection with such organisms are always present, provided that the tissues remain susceptible, the pathways of infection remain open or the possibility of stasis persists. In some of the present cases, remediable defects could not be found. Elimination of infection as early as possible in such cases is of paramount importance in order to limit the damage to the tissues and maintain renal function. Any possible means to accomplish this end is worth while. When mechanical defects are found and can be corrected, that obviously should be done. Antibacterial therapy may still have an important place before, during and after such procedures.

In the treatment of urinary tract infections the question arises whether it is the concentration of the active agent in the urine or in the tissues that is more important. The present data offer no clear answer. It would seem, however, that the concentration and other properties of the agent in the urine are of considerable significance because the greatest effect of the alkalinization must have been in the urine. It seems unlikely that the pH of the blood or of the infected tissues was altered enough to influence streptomycin activity significantly.

CONCLUSIONS

The results in the present series of cases of urinary tract infections suggest that the maintenance of an alkaline reaction in the urine throughout the period of streptomycin therapy increases the efficacy of the streptomycin and reduces the likelihood of the development of streptomycin-fastness in the infecting organisms.

REFERENCES

1. Reimann, H. A., Price, A. H. and Elias, W. F. Streptomycin for certain systemic infections and its effect on the urinary and fecal flora. *Arch. Int. Med.*, 76: 269, 1945.
2. Herrell, W. E. and Nichols, D. R. The clinical use of streptomycin: a study of forty-five cases. *Proc. Staff Meet., Mayo Clin.*, 20: 449, 1945.
3. Hirshfeld, J. W., et al. Streptomycin in the treatment of surgical infections. Report of experiences with its use. *Arch. Surg.*, 52: 387, 1946.
4. Jacobi, H. G. Streptomycin in the treatment of a case of persistent urinary infection. *New York State J. Med.*, 46: 883, 1946.
5. Petroff, B. P. and Lucas, F. V. Streptomycin in urinary infections. *Ann. Surg.*, 123: 808, 1946.
6. Committee on Chemotherapeutics and Other Agents, National Research Council. Streptomycin in the treatment of infections. A report of one thousand cases. *J. A. M. A.*, 132: 4, 70, 1946.
7. Finland, M. et al. Development of streptomycin resistance during treatment. *J. A. M. A.*, 132: 16, 1946.
8. Nichols, D. R. and Herrell, W. E. Streptomycin. Its clinical uses and limitations. *J. A. M. A.*, 132: 200, 1946.

8a. DeBakey, M. E. Discussion in ref. 8 p. 205.

9. Bondi, A., Jr., Ottenberg, D., Dietz, C. C. and Brown, C. L. Streptomycin therapy in infections of urinary tract: failure because of development of resistance. *J. A. M. A.*, 132: 634, 1946.
10. Hinshaw, H. C. and Herrell, W. E. The clinical administration of streptomycin. *M. Clin. North America, Mayo Clinic Number*, p. 855, July, 1946.
11. Knop, C. Q. Experimental study of the development of resistance to streptomycin by some bacteria commonly found in urinary infections. *Proc. Staff Meet., Mayo Clin.*, 21: 273, 1946.
12. Helmholtz, H. F. The effect of streptomycin on bacteria commonly found in urinary infections. *Proc. Staff Meet., Mayo Clin.*, 20: 357, 1945.
13. Buggs, C. W., Bronstein, B., Hirshfeld, J. W. and Pilling, M. A. The *in vitro* action of streptomycin on bacteria. *J. A. M. A.*, 130: 64, 1946.
14. Buggs, C. W., Pilling, M. A., Bronstein, B. and Hirshfeld, J. W. The absorption, distribution and excretion of streptomycin in man. *J. Clin. Investigation*, 25: 94, 1946.
15. Zintel, H. A., Flippin, H. F., Nichols, A. C., Wiley, M. M. and Rhoads, J. E. Studies on streptomycin in man. I. Absorption, distribution, excretion and toxicity. *Am. J. M. Sc.*, 210: 421, 1945.
16. Anderson, D. G. and Jewell, M. The absorption, excretion and toxicity of streptomycin in man. *New England J. Med.*, 233: 485, 1945.
17. Rutstein, D. D., Stebbins, R. B., Cathcart, R. T. and Harvey, R. M. The absorption and excretion of streptomycin in human chronic typhoid carriers. *J. Clin. Investigation*, 24: 898, 1945.

18. Hinshaw, H. C. and Feldman, W. H. Streptomycin in treatment of clinical tuberculosis: a preliminary report. *Proc. Staff Meet., Mayo Clin.*, 20: 313, 1945.
19. Hettig, R. A. and Adcock, J. D. Studies on the toxicity of streptomycin for man: a preliminary report. *Science*, 103: 355, 1946.
20. Brown, H. A. and Hinshaw, H. C. Toxic reaction of streptomycin on the eighth nerve apparatus. *Proc. Staff Meet., Mayo Clin.*, 21: 347, 1946.
21. Molitor, H. et al. Some toxicological and pharmacological properties of streptomycin. *J. Pharm. & Exper. Therap.*, 86: 151, 1946.
22. Schatz, A., Bugie, E. and Waksman, S. A. Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative bacteria. *Proc. Soc. Exper. Biol. & Med.*, 55: 66, 1944.
23. Waksman, S. A., Reilly, H. C. and Schatz, A. Strain specificity and production of antibiotic substances. v. Strain resistance of bacteria to antibiotic substances especially streptomycin. *Proc. Nat. Acad. Sc.*, 31: 157, 1945.
24. Miller, C. P. and Bohnhoff, M. Streptomycin resistance of gonococci and meningococci. *J. A. M. A.*, 130: 485, 1946.
25. Youmans, G. P., Williston, E. H., Feldman, W. H. and Hinshaw, H. W. Increase in resistance of tubercle bacilli to streptomycin: a preliminary report. *Proc. Staff Meet., Mayo Clin.*, 21. 126, 1946.
26. Wolinsky, E. and Steenken, W., Jr. Streptomycin and penicillin resistant staphylococci; influence of pH, body fluids on streptomycin action. *Proc. Soc. Exper. Biol. & Med.*, 62: 162, 1946.
27. Alexander, H. E. and Leidy, G. Influence of streptomycin on type b *Haemophilus influenzae*. *Science*, 104: 101, 1946.
28. Klein, M. and Kimmelman, L. J. The role of spontaneous variants in the acquisition of streptomycin resistance by the Shigellae. *J. Bact.*, 52: 471, 1946.
29. Graessle, O. E. and Frost, B. M. Induced *in vitro* resistance of staphylococci to streptomycin and penicillin. *Proc. Soc. Exper. Biol. & Med.*, 63: 171, 1946.
30. Sullivan, M., Stahly, G. L. and Birkeland, J. M. Reciprocal sensitivities of *Staphylococcus aureus* to streptomycin, streptothricin, and penicillin. *Science*, 104: 397, 1946.
31. Murray, R., Kilham, L., Wilcox, C. and Finland, M. Development of streptomycin resistance of gram-negative bacilli *in vitro* and during treatment. *Proc. Soc. Exper. Biol. & Med.* (in press).
32. Waksman, S. A. and Schatz, A. Streptomycin—origin, nature and properties. *J. Am. Pharm. A., Sc. Ed.*, 34: 273, 1945.
33. Loo, Y. H. et al. Assay of streptomycin by the paper-disc plate method. *J. Bact.*, 50: 701, 1945.
34. Abraham, E. P. and Duthie, E. S. Effect of pH of the medium on activity of streptomycin and penicillin and other chemotherapeutic substances. *Lancet*, 1: 455, 1946.

Dienestrol*

Another Synthetic Estrogen of Clinical Value

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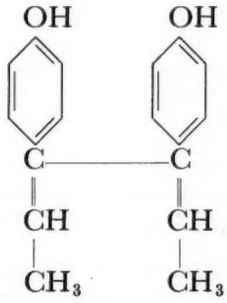
An opportunity to study the clinical usefulness of dienestrol was afforded us* in November, 1944, following brief reports of favorable results in British journals.[1,2] This synthetic estrogen is a hexadiene and it differs from the stilbestrol derivatives and from the other synthetic estrogenic materials on the American market at present. Its chemical and physical properties were recorded in 1938 and 1939 by Dodds et al.[3,4] Emmens[5] found in 1938 that its oral activity in mice was higher in relation to its subcutaneous dose than in any other estrogen yet tested. Barnes,[1] using it to inhibit lactation in women, considered that dienestrol was effective in dosage about one-tenth that of stilbestrol. Because of this known high potency per mg. the original supplies were in tablets of 0.1 mg.

The formula of dienestrol:



Our observations were made on a group of twenty-one women out-patients suffering from the complaints well known as characteristic of the climacteric syndrome. Only two had had no prior experience with estrogenic therapy. Most of them had been under observation for variable periods of time and had used one or more estrogens, natural or synthetic. Their success with other estrogens had been variable, usually satisfactory when the dose had been maintained at an adequate level. Three had had definite nausea and emesis when using barely adequate doses of diethylstilbestrol. Consequently, both clinician and patient had a basis for comparing the results following dienestrol and other estrogens. Exact dose comparisons were not made because this would have required prolonged periods of use of each substance at the minimum effective level if fair relative statements were to be made. Microscopic study of stained vaginal smears was made throughout, and the usual changes toward cornification of shed epithelial cells indicated estrogenic activity as compared with pre-treatment conditions.

The important data are presented in tabular form relating, however, to only thirteen women since eight were unable to report to the clinic regularly enough to justify conclusions about the effectiveness of the therapy. Excellent or completely satisfying results were reported by five women with doses ranging from 0.1 to 0.6 mg. daily. Seven patients secured good results but relief of

* We are glad to express our gratitude to Dr. C. W. Sondern, of the White Laboratories, Inc., Newark, N. J., for generous supplies of dienestrol.

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symptoms was not complete; doses varied from 0.1 to 0.5 mg. daily in this group. It is likely that some of this latter group would have had excellent results if circumstances had allowed us to follow them after slightly higher doses, as we did in some of the first five mentioned. An unsatisfactory result occurred in only one case and this woman preferred to discontinue trial of dienestrol at only 0.3 mg. daily.

It will be noted that in most of these women the menopause began spontaneously. The only apparent difference in results in this connection was seen in the two women whose climacteric syndromes followed irradiation and who had adequate trial of dienestrol. They secured less complete relief from the treatment than did most of our patients. In both cases there is reason to believe that the irradiation was not thorough enough to cause complete inactivation of the ovaries, a circumstance which has repeatedly seemed to cause a syndrome difficult to relieve.

Our twenty-one patients reported no nausea, emesis, nor other unpleasant side reactions from dienestrol in dosage up to 0.5 mg. twice daily, but usually not over 0.5 mg. daily. As mentioned, three patients had had nausea and emesis following diethylstilbestrol in minimum effective dosage. On the other hand, the use of dienestrol has not been followed by the spontaneous reports of well-being which were made following use of some of the natural estrogens.[6] Based on an admittedly small series, we think dienestrol is the most satisfactory synthetic estrogen with which we have had experience.

Since 0.1 mg. dienestrol secured acceptable results in only three cases and 0.2 mg. would have secured such results in six of the twelve favorable results, we suggest that the initial trial dose be 0.2 mg. and that the minimum tablet might well be this size. Similarly, since three of the twelve required 0.5 or 0.6 mg. per day, a 0.5 mg. tablet would be a convenient and probably economical size.

SUMMARY

Clinical trials of dienestrol for relief of climacteric symptoms in thirteen women indicate that doses of 0.2 to 0.5 mg. daily are adequate, dependable and tolerated without unpleasant side effects.

MENOPAUSE

Patient	Age	Spontaneous	Surgical	Radiation	Dienestrol mg./day	Results	
						Excellent	Good
Ac....	55	#			0.2		#
An....	49		#	#	0.6	#	
Er.....	29			#	0.3		#
Ha....	47	#			0.3	#	
Ke....	36	#			0.5		#
Ko....	54		#		0.3		#
Na....	53		#		0.2	#	
Re....	50	#			0.5		#
Sc.....	56	#			0.1		#
Sm....	38	#			0.2	#	
Sw....	49	#			0.1		#
Va....	31	#[a]			0.1	#	
We....	39			#	0.3		

[a] Irregular menses, climacteric symptoms.

REFERENCES

1. BARNES, J. Inhibition of lactation by synthetic estrogenic substances with special reference to dienestrol. *Brit. M. J.*, 1: 601, 1942.
2. BARNES, J. Dienestrol for menopausal symptoms. *Brit. M. J.*, 1: 79, 1944.
3. DODDS, E. C., GOLBERG, L., LAWSON, W. and ROBINSON, R. Estrogenic activity of alkylated stilbestrols. *Nature*, 142: 34, 1938.
4. DODDS, E. C., GOLBERG, L., LAWSON, W. and ROBINSON, R. Synthetic estrogenic compounds related to stilbene and diphenylethane. *Proc. Roy. Soc. B.*, 1927: 140, 1939.
5. EMMENS, C. W. The oral activity of certain androgens, oestrogens and augmenting substances. *J. Physiol.*, 94: 22P, 1938.
6. SEVRINGHAUS, E. L., and ST. JOHN, R. Oral use of conjugated estrogens-equine. *J. Clin. Endocrinol.*, 3: 98, 1943

Review

Bacillus Pyocyaneus Infections*

A Review, Report of Cases and Discussion of Newer Therapy Including Streptomycin†

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DURING the last four years penicillin has been used in clinical medicine and surgery in increasing amounts, not only for the treatment of infections due to gram-positive organisms but also as "prophylactic" therapy in an attempt to *prevent* infection. This period has been marked by a growing number of cases of secondary infections due to such gram-negative organisms as the B. pyocyaneus. This did not occur during the sulfonamide era because these latter drugs are much less specific in their bacteriostatic properties and tend to prevent the growth of gram-negative bacilli. On the other hand, a relatively minor contamination with gram-negative organisms in a patient treated only with penicillin will often be followed by a flourishing infection; as one of an apparently mutually antagonistic pair is efficiently removed, the other thrives. We are now beginning to see the converse of the same situation; as the equally specific antibiotic streptomycin is being widely used more and more unexpected infections with gram-positive organisms are discovered.[149]

It is the purpose of this paper to review the subject of infection with the B. pyocyaneus. This seems to be a particularly appropriate time for such a summary, not only because it is a short while after the introduction of streptomycin, another agent effective in treatment, but also because the results of approximately ten years' experience in the use of the sulfonamides are now available. We are reporting several cases in which we have treated the patients with each of these agents.

LITERATURE

Since the isolation of the B. pyocyaneus in 1882 by Gessard[1] the literature has not been extensive and in general has been commensurate with the frequency with which the organism is found as a human pathogen. Most of the articles consisted of case reports of various types of infections. In Fraenkel's classic paper[2] the general pathological picture was graphically portrayed. General reviews of the subject were written by Waite[3] (older literature to 1908) and more recently by Lode[4] (1929) and Epstein and Grossman[5] (1933). Other reviews of localized infections, endocarditis (Fish, Hand and Keim,[48] Moragues and Anderson[50]), meningitis (Evans,[58] 1936), gastrointestinal infections (Bezi,[37] 1933), corneal ulcer (Joy,[115] 1942), etc., are available.

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† Examinations of the pathological material were carried out by Dr. Rudolph Osgood (Cases II, III, IV and X) and Dr. Charles Branch (Case I).

BACTERIOLOGY[4,6,7]

The B. pyocyaneus (Ps. aeruginosa, Ps. pyocyanea, Bacterium aeruginosum) is a slender gram-negative rod 1.5–3.0 by 0.5 micra which exhibits considerable variation in morphology and cultural characteristics. It is motile, non-sporing and non-acid-fast. It grows readily on the usual media at optimum temperatures of from 30–37°c. and pH from 6.6 to 7.0. It is aerobic and forms acid from glucose but from no other sugar; no gas is produced from carbohydrate fermentation. Some strains produce two pigments,[8,9,10] pyocyanin (blue, soluble in water and chloroform) and fluorescin (yellow or green, fluorescent, soluble in water, insoluble in chloroform). Other strains produce only one of these pigments and a few are entirely colorless. Old cultures may change from bluish-green to reddish-brown, black or yellowish-brown as oxidation alters the chemical structures of the pigments. The organism has been called "the bacillus of blue-green pus"[1] because of this characteristic discoloration which is imparted to exudates by its pigments.

The organism produces a proteolytic enzyme which enables it to hydrolyze gelatin, fibrin, casein and albumen. This, together with the characteristic site of localization of the organisms in the smaller blood vessels with consequent thrombosis and occlusion, partly explains the tendency to production of infarct-like areas of necrosis with a minimum of inflammatory reaction which has been so frequently noted.[2]

B. pyocyaneus is capable of exciting production of various antibodies in infected animals and man. Of these the agglutinins are the best studied. They appear early, are easily identified and hence are of definite diagnostic value. A titer higher than 1:30 is rarely encountered in normal subjects,[11] while titers as high as 1:500–1000 are common in the presence of infection. Owing to the great variation in antigenicity the patient's own strain of organisms should be used as the agglutinogen.

B. pyocyaneus is found on the normal human skin, particularly in the axillary and anogenital regions,[4] and is uncommonly cultured from the stool.[11,12] It may be grown from the air, especially in surgery wards containing patients with infected wounds.[101] In some sections of the world it is easily discovered in the drinking water which thus provides it an easy access to the gastrointestinal tract.[11] It may contaminate solutions of penicillin,[101] boric acid,[132] fluorescein,[120] procain[28] and other anesthetic agents (see section on meningitis) and "sterile" distilled water and thus be carried to a favorable location for initiation of infection.

The problem of contamination of penicillin solutions by resistant organisms is a real one;[101] there is always danger of secondary infections, as when the agent is used for intrathecal injection in the treatment of meningitis or for instillation into the various serous cavities. One occasionally encounters an instance of abscess formation at the site of injection in the muscle which has a similar pathogenesis. Strict asepsis must be maintained in the preparation and injection of penicillin solutions.

PYOCYANEUS SEPSIS

It is now firmly established that the B. pyocyaneus may invade the blood stream and produce sepsis although it should be emphasized that its usual rôle is that of a relatively avirulent secondary contaminant in superficial wounds. The first reports of cases in which positive blood cultures were found during life were those of Finkelstein[13] (1896) and of Brill and Libman[14] (1899). Bacteremia most frequently occurs in infants and children and in adults afflicted with chronic debilitating diseases. Cases (I, II, III, IV and IX) described in this paper are excellent examples of adult infections in which the B. pyocyaneus sepsis occurred as a termi-

nal complication in patients already ill with fatal diseases. In infants and children,[2,39] the skin is most commonly the portal of entry for the organism; in adults invasion is also frequently through the genitourinary tract.[42–45] The gastrointestinal tract is the site of entry in a considerable number of patients, both infants and adults. Enteric infection which, contrary to the usual predilection, may be present in otherwise healthy adults, may produce a clinical picture which is indistinguishable from that of typhoid fever except for its short duration and almost invariably benign course.[15,16]

There are interesting reports of sepsis arising in unusual locations. Wassermann[17] described an epidemic of eleven cases of umbilical infection of the newborn all of which resulted in death. Several cases of postpartum infection with bacteremia[18,19,55] have been reported. Kraus and Hunter[97] reported a case apparently of infection of the fetus through the placenta. The mother had chills and fever during labor; the baby was born with a rash and died twenty hours after birth with sepsis. The mother had B. pyocyaneus in her stools, but not in the lochia; no blood cultures were taken during the chills.

The clinical picture in sepsis due to the B. pyocyaneus is usually not different from that produced by many other types of organisms, and the diagnosis is of necessity based on culturing the bacillus from the blood. There are chills, high fever, prostration, petechial skin lesions, jaundice and embolic manifestations in various organs including splenomegaly, just as in any septic infection. Agranulocytosis, with or without angina,[20–24] has been observed occasionally and has been the subject of several special reports. Secondary thrombocytopenic purpura with resulting hemorrhages[26] may complicate the picture, as in our Case II (H. B.). There is one phenomenon, however, which when it occurs during the course of an apparent sepsis should lead one to suspect strongly the causative rôle of the B. pyocyaneus on clinical grounds. This is the finding of gangrenous skin lesions ("ecthyma gangrenosum"),[22,25,137] particularly in the anogenital region and the axillae. Fraenkel[2] was able to make the diagnosis clinically from the presence of these lesions with a high degree of accuracy.

The course is generally rapidly downhill, with the exception cited,[15,16] and usually terminates fatally[2] despite treatment. In all likelihood this is as much an indication of the general debility of the usual patient as it is of the virulence of the organism. Secondary localization of infection, particularly in the meninges and on the heart valves, may add other symptoms which complicate the clinical picture.

CASE I. Pneumococcic pneumonia and empyema were present in a woman with paraplegia who was debilitated, bedridden and incontinent. (Fig. 1.) B. pyocyaneus infection in large decubitus ulcers and later development of gangrenous cystopyelonephritis and sepsis due to B. pyocyaneus were followed by death.

R. K., a fifty-two-year-old female, entered on December 26, 1944, complaining of a cough productive of yellow, thick sputum of six weeks' duration, and bilateral decubitus ulcers of more than two months' duration.

Four years prior to admission she entered the hospital with ataxia, paresis of the lower extremities and incontinence of urine and feces of one year's duration. There were vague sensory disturbances and nystagmus. She signed herself out before a definite diagnosis was made, although multiple sclerosis was considered the best possibility. She remained at home, bedridden and incontinent, until the present admission.

Six months prior to admission, following a head cold, she developed a cough which soon became productive of thick, yellow sputum, occasionally blood-flecked. There were no chills, sweats or pleuritic pains. No specific treatment was given. During the month prior to admission the cough became worse and progressive or-

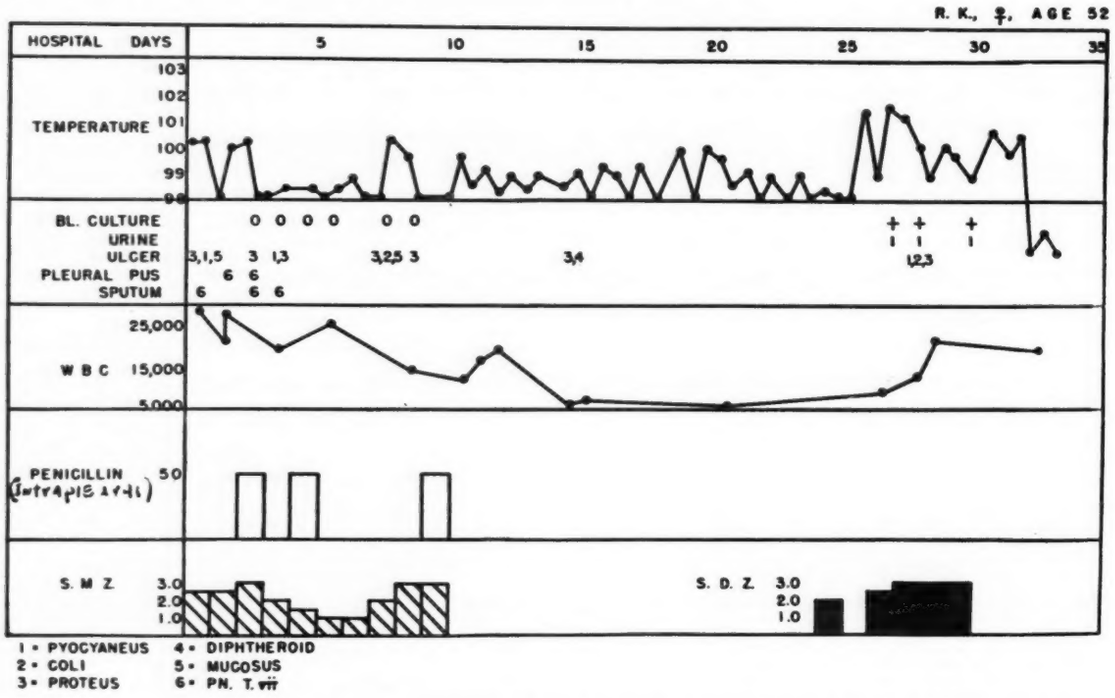

FIG. 1. Case 1. Infection with B. pyocyaneus in large decubitus ulcers followed by gangrenous cystopyelonephritis and fatal sepsis.

thopnea developed. Because of the orthopnea and incontinence, she spent the two weeks before coming to the hospital sitting on a special rocking chair with a built-in toilet seat. During this period, two previously small bed sores on her buttocks became much larger and more painful. She developed marked stubbornness, occasional delirium and frequent crying spells. One week before admission, she began to have marked edema of the lower extremities.

Physical examination revealed the patient to be well developed but emaciated and she appeared chronically ill. She preferred to lie on her side with her lower extremities flexed on her abdomen. On each buttock was a large ulcer, 7 to 8 cm. in diameter, with a purplish-black, necrotic, sloughing center and red, swollen, tender periphery. There were flatness to percussion and distant bronchial breath sounds at the left base, posteriorly, with shift of the mediastinum to the right. The heart was otherwise normal. The abdomen was normal. There was marked soft pitting edema of the lower extremities. There was a right horizontal nystagmus. Paralysis of the lower extremities with flexion contracture was present. Deep tendon reflexes were absent in the lower extremities but normal in the upper extremities. Abdominal reflexes were absent. There was no Babinski. There was marked emotional lability but the sensorium was clear.

Pneumococcus type VII was cultured from the sputum and the thick, green pus aspirated from the left pleural cavity. There was a slight albuminuria, with marked pyuria, and slight microscopic hematuria throughout. B. pyocyaneus, B. coli and B. proteus were cultured from the urine during the latter part of the course. The white blood count on admission was 29,400 per c. mm., with 72 per cent polymorphonuclear leukocytes. There usually was a well marked leukocytosis, ranging from 13,000 to 26,000 white blood cells per c. mm. of blood, although during the eleven days prior to the development of the pyocyaneus bacteremia, which preceded death, the white blood count was essentially normal. A moderate anemia persisted, with hemoglobin ranging from 11.5 to 8.5 Gm. per cent, and hematocrit from 32 to 25 per cent. There was a mixed flora in the decubitus ulcers; B. pyocyaneus, B. coli and B. proteus were the principal organisms. During the latter part of the course, B. pyocyaneus predominated in the cultures.

Treatment of the pneumococcus pneumonia in the hospital was begun with sulfamerazine by mouth and was continued for nine days. Great difficulty was experienced in obtaining an adequate fluid intake. The empyema was treated by repeated aspirations of the pus and instillation of penicillin into the pleural cavity. Gradual débridement of the decubitus ulcers was carried out with repeated irrigation of the craters with a solution containing a mixture of 10 per cent urethane and 1 per cent sulfanilamide. With this therapy she seemed to improve somewhat, although she was drowsy usually and required tube feeding. The ulcers cleared considerably, the necrotic tissue being eliminated, and presented moderately clean contracting granular bases. A Foley catheter was inserted into the bladder soon after admission. Because of a dilated urethra, there was some difficulty in preventing spontaneous extrusion of the inlying catheter from the bladder. On the twenty-third hospital day, she complained of severe, lower abdominal, steady pain. Two days later, a small amount of gross blood and pus was noted draining from the bladder. The following day she began to run a rapidly downhill course, characterized by spiking fever, jaundice, increasing stupor and repeated vomiting of coffee-ground material. B. pyocyaneus was cultured from the blood on three different days. Nitrogen retention developed. On the thirty-second hospital day, a right anterior pleural friction rub was noted. She died on the thirty-fourth hospital day after a terminal fall in body temperature to 95 and 96°F.

Gross Pathology. Kidneys: The right kidney weighed 260 Gm. and was distinctly enlarged. The capsule was slightly thickened, stripped with ease, revealed a grossly irregular, finely granular, reddish-brown surface, marked by several varying-sized, elevated areas containing numerous minute, white, elevated foci, which, on section, were found to extend down through the cortex to involve the pyramids in radial streaks. Section revealed an edematous, bulging surface everywhere marked by the white radial streaks. From the pyramids a small amount of purulent material was expressed. The mucosa of the pelvis was roughened and necrotic. The pelvis contained a small amount of sanguineous pus. The ureter was dilated and measured 6 mm. in diameter. No ureteral obstruction was found.

The left kidney weighed 300 Gm. Externally it closely resembled its fellow on the right. On section, two entirely separate pelves and ureters were found. The upper pelvis and its ureter were normal. The mucosa of the lower pelvis was gangrenous with a large amount of hemorrhage in the tissues. The renal substance on the left resembled that on the right. The two ureters entered the bladder through separate orifices.

Urinary Bladder: The mucosa was markedly hemorrhagic and necrotic. There was approximately 20 cc. of bloody pus in the bladder.

Pleural Cavities: The right was completely obliterated by fibrinous adhesions which were easily separated. The left was completely obliterated by very dense adhesions which were separated only by sharp dissection. At the posterior base there was a cavity 10 cm. in diameter from which air under pressure escaped when opened. The lining of the cavity was fibrinous. No bronchial communication was found.

Gastrointestinal Tract: On the greater curvature of the stomach there was a shallow superficial ulceration of the mucosa, 8 mm. in diameter. The base was clean and there was no necrotic membrane. No other lesions were seen in the gastrointestinal tract.

The lungs, heart, and other organs were not remarkable grossly.

The predominating organism cultured from the urinary tract and empyema cavity was B. pyocyaneus.

MICROSCOPIC PATHOLOGY. *Urinary Bladder:* The mucosa was almost completely replaced by a heavy infiltration with polymorphonuclear leucocytes and fibrin. There were many large colonies of organisms in this membrane. There was extensive thrombosis of the capillaries overlying the muscularis. The muscularis was edematous and the muscle fibers fragmented in several places; slight infiltration with neutrophiles extended into the superficial layers of the muscularis.

Kidneys: The pelves resembled the urinary bladder. Approximately four-fifths of the kidneys themselves were completely destroyed, riddled with extensive discrete and confluent abscesses, which extended in a radial fashion

from the pelvis, and which obliterated the normal architecture. Much of the remaining tissue was edematous and in a state of semi-liquefaction necrosis, with slight neutrophilic infiltration from adjacent areas of suppuration. Numerous vessels contained bacteria-laden thrombi, especially near the pelvis.

Stomach: Section through the ulcer showed that the normal mucosa abruptly gave way to the shallow crater which extended only to the muscularis. The base of the ulcer was covered with a thin network of fibrin, in which there were many neutrophils and colonies of bacteria. There were no thrombi or emboli in the vessels immediately underlying this area, although the general histological appearance strongly suggested an embolic origin. The muscularis was edematous and the overlying serosa was normal.

Lungs: In general, the alveoli contained only a small amount of coagulated albuminous precipitate in which were very few inflammatory cells. Occasional small vessels were completely occluded with masses of disintegrating fibrin, neutrophils and large colonies of bacteria. In such areas the vessel walls were partially or completely destroyed by an acute inflammatory and necrotic process, and the surrounding alveoli were distended with large numbers of neutrophils and erythrocytes, fibrin and colonies of organisms. There was a small amount of neutrophile-laden mucus in the bronchi and slight edema and infiltration of the walls.

Spleen: Very little of the normal structure remained. There were extensive capillary thromboses, surrounded by zones of coagulation and liquefaction necrosis, heavily infiltrated with polymorphonuclear leukocytes, macrophages and some lymphocytes. There were scattered hemorrhages and much fibrin present. Many small colonies of organisms were seen in the thrombosed vessels and areas of necrosis.

Liver: The liver cells were swollen, stained faintly and acidophilically with poorly defined nuclei. This property was more marked about the central veins; about these vessels there was early necrosis, with only occasional patches of beginning neutrophilic infiltration.

Other changes included slight hypertrophy of the myocardium with moderate coronary atherosclerosis and myocardial fibrosis, and in the adrenals, small areas of focal necrosis and multiple small infected emboli.

Final Pathological Diagnoses: Acute ulcerative cystitis; acute bilateral pyelonephritis; B. pyocyaneus septicemia, with embolic lesions in the lungs, spleen, stomach and adrenals; encapsulated thoracic empyema, left; early central necrosis of the liver and bilateral advanced decubitus ulcers. (Sections of the brain and spinal cord were not available at this time so that the primary central nervous system lesion is unknown.)

Case II. This is a case of B. pyocyaneus septicemia occurring during treatment with penicillin for secondary infection of the skin in a boy with an acute exacerbation of chronic disseminated lupus erythematosus. (Fig. 2.) Sterilization of the blood stream was carried out with streptomycin. Congestive heart failure, thrombocytopenic purpura and meningitis were followed by death.

H. B. was a seventeen-year-old schoolboy who was transferred from a neighboring hospital with a progressive generalized weeping, crusted rash and high fever. The family history and past history were irrelevant.

Two years prior to admission he developed an area of erythema of "butterfly" distribution over both cheeks and bridge of the nose, which persisted for several months despite various local applications and injections of bismuth subsalicylate intramuscularly. Nineteen months prior to admission, while the lupus erythematosus was still active, he was given sulfathiazole and later sulfamerazine for a dental abscess. He reacted to these drugs with fever, nausea and vomiting. After extraction of the offending teeth, there was oozing of blood from the gums for two weeks. Following this, however, he improved and the rash virtually disappeared in a short time. Sixteen months prior to admission, a tonsillectomy was also followed by a small amount of bleeding from the fossae for several weeks. There were no other manifestations of a hemorrhagic tendency.

Five months prior to admission, he incurred a severe generalized sunburn. A recrudescence of the lupus erythematosus quickly developed, and the rash spread to the forehead, ears, scalp, neck and back. During the next three months, the process persisted despite treatment and the hands

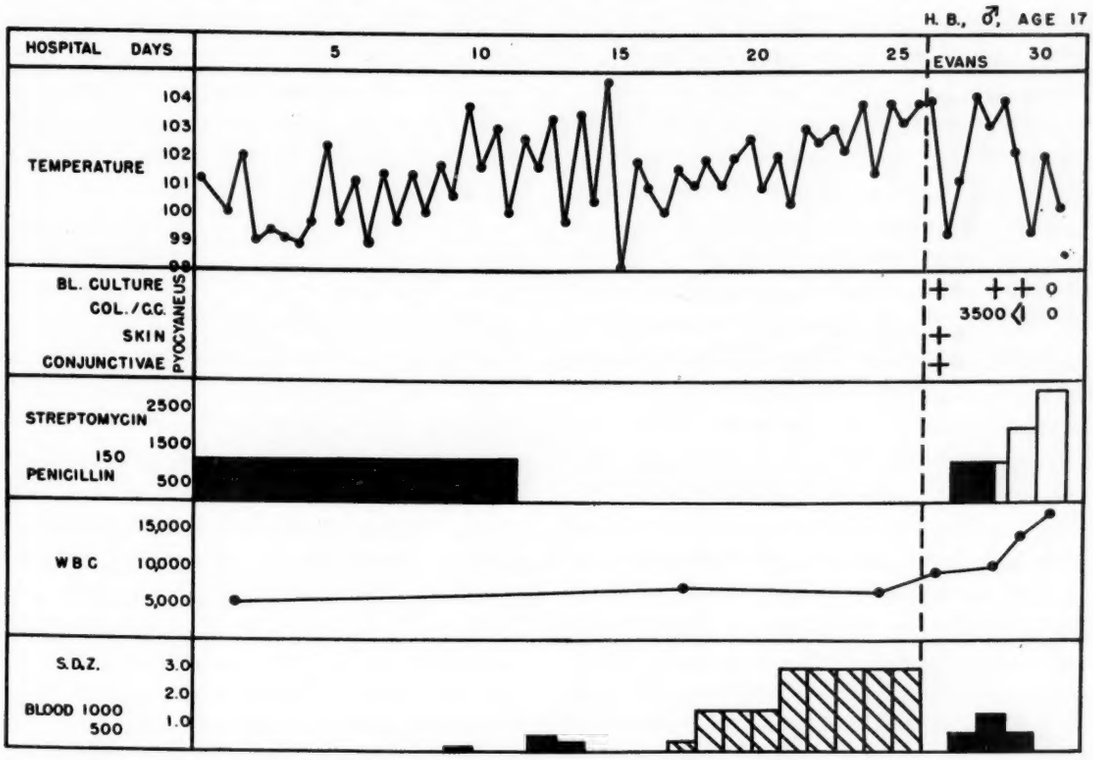

FIG. 2. Case II. Fatal septicemia with onset during penicillin treatment for secondary skin infection in chronic disseminated lupus erythematosus.

and fingers became involved. Seven weeks prior to admission, after considerable scratching because of pain, burning and itching, the rash became weeping and crusted. Irregular fever as high as 102°F. persisted.

Twenty-six days prior to admission he entered the referring hospital. He was febrile but only "moderately" ill. There were crusted, weeping papular lesions, 2 to 10 mm. in diameter, scattered over the anterior surface of the chest, neck and hands. A similar, but more pronounced and confluent rash covered the face, ears and scalp. The mucous membrane of the nose was edematous, red and bleeding. The soft palate was covered with discrete, oozing, red papules resembling the skin lesions. There was a moderate anemia and normal white blood cell count.

Penicillin, 160,000 units daily, was administered for eleven days, with only temporary benefit in the beginning. During the last week in this hospital, sulfadiazine in small doses was given. He received three small transfusions, totaling 650 cc. of whole blood. He continued to run a septic temperature, his skin lesions were progressive and his general condition grew worse.

On admission to the Evans Memorial he appeared emaciated, debilitated and severely ill. The lesions on the face, scalp and ears were covered with sanguino-purulent exudate, much of which was dried and crusted. There was marked edema of the face, especially of the periorbital regions. There was a purulent conjunctivitis; the eyes were swollen shut. There were numerous 4 to 5 mm. vesicles filled with serous or serosanguineous fluid on an erythematous base scattered over the chest, abdomen, upper extremities, thighs and flanks. The palmar surfaces of the hands and fingers and the V-area of the neck were covered with painful erythematous papules, often confluent. The nails were broken. There was subungual infection. The mucous membranes of the nose and mouth were crusted and bleeding so that examination was inadequate. The lungs were normal. There was a marked sinus tachycardia (rate 150) with a pronounced diastolic gallop. The heart was of normal size and there were no murmurs present. Blood pressure was 104/54 (left arm). The abdomen was normal. There was moderate bilateral

costovertebral tenderness. There were no neuromuscular abnormalities; the neck was supple.

Urine averaged 6 Gm. per liter of protein (4+), contained no sugar, ketones or bile. There were 5 to 30 leukocytes and 5 to 30 erythrocytes per "high-dry" microscopic field (uncentrifuged specimens). Granular, erythrocytic and leukocytic casts were present in large numbers. Hematocrit was 19.5 per cent and hemoglobin 5 Gm. per cent. Four days later, as a result of transfusions, these had risen to 42 and 13.2 Gm. per cent, respectively. Total leukocytes in the blood were 9,800 per c. mm. with 75 per cent polymorphonuclears, 17 per cent lymphocytes and 8 per cent monocytes on admission, and steadily rose to 17,300 four days later. Blood platelet counts varied from 41,000 to 67,000 per c. mm. Blood clotting time (3-tube method) was twelve minutes, forty-five seconds (normal six to twelve minutes). Bleeding time (Duke method) was two minutes, forty seconds. (This procedure was probably inaccurate because of inability to find a skin area completely free of lesions.) Clot retraction was 47 per cent of plasmatocrit (normal 80 per cent or more). Blood non-protein nitrogen was 47 on admission, and steadily rose to 108 on the fourth day. Blood total proteins were 6.2 Gm. per cent, with 1.25 Gm. albumin and 4.96 Gm. globulin on admission. Carbon dioxide combining power varied from 29 to 39 volumes per 100 cc.

Three blood cultures were positive for B. pyocyaneus. On the second day, when treatment with streptomycin was begun, there were 3,500 colonies per cc.; one day later there was less than one colony per cc. On the third day of treatment, the blood culture was sterile (day of death). B. pyocyaneus was cultured from the pus in the conjunctival sacs and from several of the skin lesions.

Bedside chest *x*-ray on the second day revealed suggestive evidence of cardiac enlargement and patches of hazy density radiating from the hilar regions to both mid-lung fields.

Electrocardiogram on the second day showed a sinoauricular tachycardia of 150 beats per minute, low voltage and slurring of the Q-R-S complexes, inversion of the T waves in leads 1 and 2, and a normal axis. Two days later there was moderate right axis deviation, the T waves in lead 1 were upright with slightly high origin, and there was a Q wave in lead 1.

Streptomycin, 250,000 units every three hours subcutaneously, was started approximately forty hours after entry, after the nature of the bacteremia became known. The dosage was increased to 500,000 units every three hours ten hours before death. A total of 5,810,000 units was given. Ten doses of penicillin, 20,000 units every three hours intramuscularly, were given early in the course, before the blood culture report had been received, but this was discontinued when streptomycin was started.

Supportive treatment consisted of 2,000 cc. of whole blood, in four transfusions of 500 cc. each, intravenous and subcutaneous fluids in the form of physiological saline and 5 per cent glucose solutions, and oxygen by means of a tent and nasal catheter. Warm saline compresses were followed by the application of aquaphor to the skin lesions several times daily. The conjunctivae were irrigated with a streptomycin solution, 5,000 units per cc., in physiological saline. Cedilanid (lanatoside C) was given in five doses of 0.4 mg. each intravenously on the second day, when it appeared that congestive heart failure was present, and was continued in maintenance doses until death.

During the period at the hospital before the exact diagnosis was known, he steadily grew worse and became irrational and semi-stuporous. Temperature, which was 99°F. rectally on admission had risen to 104.2°F. twenty-four hours later. The skin lesions tended to spread and he became cyanotic and dyspneic. On the second day, when a large subcutaneous ecchymosis appeared on the abdominal wall within a very short time, and later that day the skin lesions began to assume a hemorrhagic appearance, it became evident that thrombocytopenic purpura was present. Within twenty-four hours after streptomycin was begun on the second day his temperature returned to normal, the skin lesions improved dramatically, with much decrease of exudation and inflammatory reaction. However, the dyspnea still persisted, there was a disproportionate tachycardia and only slight improvement in his responsiveness. On the fifth day the rectal temperature rose secondarily to 102°F., the heart rate continued at 140 beats per minute

and he began to complain of headache. Shortly thereafter he died suddenly, apparently of ventricular asystole, approximately one hundred hours after admission.

GROSS PATHOLOGY. *Pleural Cavities:* The left pleural cavity contained 300 cc. of turbid fluid, and the right 200 cc. of similar fluid.

Pericardial Cavity: This cavity contained 200 cc. of clear yellow fluid.

Heart: The heart weighed 320 Gm. and was somewhat enlarged with dilatation of the right atrium. Situated on the leaflets of the mitral valve were several small verrucae, which were yellow in color and firm in consistency, measuring less than 0.5 mm. in diameter. There was no ulceration of the valve leaflets and the other valves were normal.

Lungs: The right lung weighed 640 Gm. There was normal crepitation at the apex. The middle and lower lobes were congested and of firmer consistency. The cut surface of the lower and middle lobes appeared deep reddish-gray and moist, exuding a moderate amount of fluid on pressure. The left lung weighed 590 Gm. The lower lobe was quite congested and when cut presented a red, moist surface which exuded fluid on pressure.

Liver: The liver weighed 1,940 Gm. It was of firm consistency and on cut section presented a reddish-brown, slightly granular appearance.

Kidneys: The right kidney weighed 180 Gm., the left 190 Gm. External surfaces were smooth, reddish-brown and glistening. Coronal sections revealed numerous small, petechial, hemorrhagic areas throughout the cortex and medulla, measuring less than 1 mm. in diameter.

Brain and Meninges: A small amount of purulent exudate covered the cortex and extended to the base.

MICROSCOPIC PATHOLOGY. *Heart:* There were scattered areas of old scarring and isolated focal areas of acute myocardial necrosis, with increased vascularity and accompanying collections of polymorphonuclear neutrophiles and lymphocytes. A section through the mitral valve showed the pink collagenous tissues of the leaflet; attached to it was a broad-based, papillomatous nodule of lighter staining, fibrous tissue covered by endothelial cells. No colonies of organisms were seen.

Lungs: The alveolar spaces in large areas were filled with serum precipitate with very little cellularity. Especially near the lung bases were spotty areas of acute inflammatory reaction involving small bronchioles as well as alveoli. There was pronounced congestion of the pulmonary vessels but no demonstrable thrombi.

Spleen: There was marked congestion with the number of polymorphonuclear neutrophiles and macrophages also increased. Scattered foci of heavier infiltration with neutrophiles occurred.

Liver: There was moderate fatty infiltration. Occasional scattered foci of necrosis infiltrated with polymorphonuclear leukocytes predominantly were found.

Kidneys: The typical "wire loop" appearance was seen in the glomerular tufts. In addition, there was a varying degree of acute necrosis of other glomerular tufts with accompanying polymorphonuclear infiltration, hemorrhage and fibrin thrombi. Fairly extensive focal interstitial hemorrhages and hemorrhages into the tubules were found. The tubular epithelium of the cortex showed granular swelling and degeneration. There were scattered foci of chronic inflammatory cells, particularly in the cortical areas; frequently there were radial streaks of inflammatory cells along the tubular interstitial tissue. Focal areas of hemorrhagic necrosis were occasionally noted in the cortex, involving groups of tubules, a glomerulus and blood vessels. The latter showed hemorrhage and necrosis of their walls. No bacteria were seen.

Thyroid Gland: Numerous areas of acute necrosis with heavy infiltration with neutrophiles, lymphocytes and erythrocytes occurred. Some of the blood vessels in these foci were partially occluded by hyaline thrombi; the walls showed slight degenerative change and infiltration with a few red blood cells and polymorphonuclear leukocytes. No organisms were found.

Skin: An intradermal vesicle was filled with masses of erythrocytes, a small amount of fibrin, a few polymorphonuclear leukocytes, macrophages and many small clusters of bacteria, mostly bacilli. Another section revealed degeneration and necrosis of the epidermis and adjacent corium, and infiltration with a moderate number of polymorphonuclear leukocytes. The blood vessels were congested but no definite

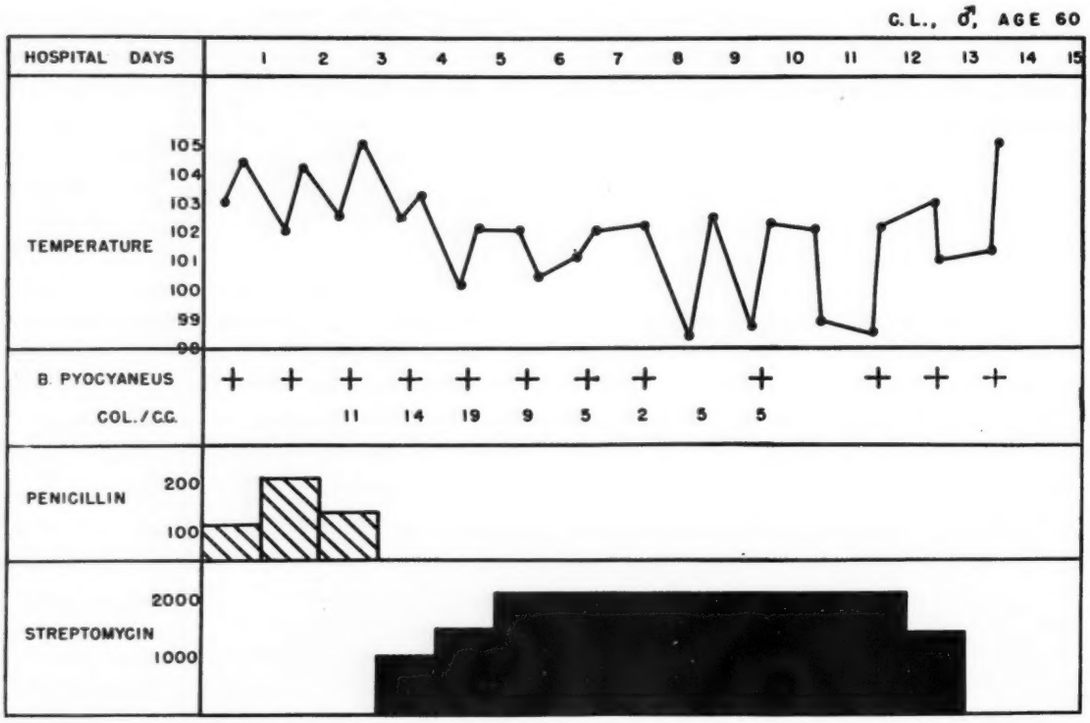

FIG. 3. Case III. Fatal sepsis during chronic lymphatic leukemia, with rapid development of resistance of the organism to streptomycin.

thrombi were found; no bacteria were seen in these areas.

Sartorius Muscle: There were numerous hemorrhagic areas in the muscle bundles, which widely separated them. Foci of degeneration and necrosis of the bundles were frequent. Within or near the hemorrhagic lesions were numerous engorged blood vessels with necrotic walls and extravasation of red blood cells and infiltration with polymorphonuclear leukocytes and large mononuclear leukocytes. Some of the smaller vessels were partially or completely occluded with thrombi, composed of masses of fibrin and polymorphonuclear leukocytes. Some of the vessels showed deep blue staining fibrin masses in their walls and deeply staining swollen collagen fibers. Throughout the hemorrhagic areas there was diffuse infiltration with polymorphonuclear leukocytes. No definite bacteria were found.

Brain: Sections from the base of the brain and through the cortex showed purulent exudate in the subarachnoid space, consisting of polymorphonuclear leukocytes, macrophages and a few lymphocytes. Occasional gram-negative bacilli were seen in the areas of inflammation. There were no inflammatory lesions of the nervous tissue.

Cultures: From the lungs, heart, blood, etc., there was no growth. Unfortunately, the meningeal exudate was not cultured.

Final Pathological Diagnoses: Chronic disseminated lupus erythematosus; B. pyocyaneus septicemia with terminal meningitis, and acute and chronic myocarditis with terminal congestive heart failure.

CASE III. This was a case of B. pyocyaneus septicemia with ulceration of the rectum in a man with chronic lymphatic leukemia. Streptomycin therapy was ineffective because of rapidly developing resistance of the strain of organisms and death followed. (Fig. 3.)

C. L. was a sixty-year-old, white male who was admitted for the first time to the Evans Memorial on October 8, 1945, complaining of weakness and dyspnea on exertion of three weeks' duration, slight anorexia of the same duration, and a weight loss of 10 to 12 pounds during the preceding six months. Following extraction of two teeth two and a-half weeks prior to admission, there was apparently local infection which had not subsided on admission.

Physical examination revealed the patient to be a pale, chronically ill but obese man. Several small ecchymoses were seen on the buccal mucous membrane. There were many flame-shaped hemorrhages in both fundi, with an especially large hemorrhage into the right fovea centralis. The remaining few teeth were carious, loose and there was marked pyorrhea alveolaris present. The spleen was slightly enlarged, being barely palpable. There was no lymphadenopathy.

The urine was normal. There was a marked anemia, the erythrocyte count being 1,770,000 per c. mm. with hematocrit of 19 per cent, hemoglobin 6.2 Gm. per cent, M.C.V. 107 cubic micra, M.C.H. 35 gamma gamma, reticulocytes 2.5 per cent. Total white count was 4,000–8,150 per c. mm. with 8 per cent polymorphonuclear leukocytes, 88 per cent lymphocytes (2 per cent atypical) and 4 per cent monocytes. Thrombocytes were 187,000 per c. mm. Bleeding time averaged eight minutes, clotting time five and a-half minutes. Clot retraction was 49 per cent of plasmatocrit (normal 80 per cent or more). Tourniquet test produced 17 petechiae per square inch (normal less than 15). Sternal puncture revealed the marrow to be infiltrated with lymphocytic elements.

During the first twelve days in the hospital, he received 3,000 cc. of whole blood and 900 cc. of washed red cells. Several febrile reactions occurred, one of which followed extravasation of blood into the left forearm, with swelling, redness and heat. He was treated with penicillin for this, though no etiological agent was ever demonstrated. He was discharged on the seventeenth day, October 25th, markedly improved, with near-normal blood levels. Diagnosis was chronic lymphocytic leukemia, aleukemic stage, myelophthisic anemia and dental caries with pyorrhea alveolaris.

Thirty-nine days after discharge, he was readmitted (December 3, 1945) with the complaints of recurrent weakness, pain and swelling in the lower jaw and insomnia, all of one week's duration. During the three weeks prior to readmission, he had fourteen teeth extracted in two sittings, which were followed by fever up to 102°F., pain and swelling in the jaws and face and several severe bouts of epistaxis.

Physical examination revealed no essential change except a further weight loss of eight pounds since discharge, complete edentulousness without evidence of infection at the sites of extraction, several small ecchymoses in the skin of the shoulders and arms and a small superficial ulcer at the right base of the tongue.

Laboratory examination showed that there was a severe anemia, with hematocrit of 18 per cent and hemoglobin of 6.1 Gm. per cent. The total white blood count was unchanged, with 7,900 leukocytes per c.mm. 4 per cent polymorphonuclear leukocytes, 95 per cent lymphocytes and 1 per cent monocytes.

In the hospital, multiple transfusions, a total of 2,000 cc. of whole blood and 2,000 cc. of washed resuspended red cells, were given, with an increase in hemoglobin to 10.2 Gm. per cent and in hematocrit to 31 per cent. A small abscess developed on his neck following a cut from a razor; this was treated with local heat and appeared to be healing well when he was discharged on December 12, 1945, nine days after admission.

Five days later, on December 17, 1945, he was readmitted with the complaints of chills, fever and sweats of three days' duration, and an increase in the size and number of the "boils" which he had when he left the hospital. Oral temperature was 103.5°F., pulse 96, respirations 12 per minute, and blood pressure 118/56. He was acutely ill, weak and irritable, but with slightly clouded sensorium. There were many cutaneous petechiae of generalized distribution. Several small superficial abscesses were present on the skin of the neck. At the right submandibular area there was a large (6 by 4 cm.) hot, red, swollen, indurated area in the skin and subcutaneous tissues. A large area of second degree burn (hot water bottle) was present on the skin surrounding the anus and on both buttocks. Exquisite pain was produced by insertion of the finger into the rectum but no ulceration was felt at this time. An anemia similar to that on previous entries was noted with a similar leukocyte count. B. pyocyaneus was cultured from the blood daily. This organism, along with others including the hemolytic staphylococcus aureus, was cultured from the blistered areas on the buttocks.

In the hospital, his temperature ranged from 102 to 105°F. during the first three days with a corresponding pulse. Penicillin had been administered pending the blood culture reports; on the second day this was discontinued and streptomycin was begun in the dosages indicated. During the next week, although his temperature was slightly lower, ranging from 100 to 103°F., his general condition grew worse. There was a progressive anemia and leukopenia, for which he was given 2,000 cc. of whole blood. He became incontinent of urine and feces. He was frequently stuporous. Large ecchymoses developed in the skin of his left arm and chest. The abscess in the neck continued unchanged. There was such extreme tenderness in the anal and perineal regions that a digital rectal examination was impossible. He began to cough up small clots of blood frequently. Dyspnea and cyanosis developed which were relieved only partially by oxygen by mask. On December 29, 1945, after nearly ten days of administration, the streptomycin was discontinued. The persistence of the B. pyocyaneus bacteria corroborated the insensitivity of the organism to the antibiotic *in vitro*. (Growth of this strain of B. pyocyaneus was not inhibited by a concentration of 500 units of streptomycin per cc. of media.) A total of 19,150,000 units of streptomycin was given. On the fourteenth hospital day, there was a rise in temperature to 105°F. He died quietly on December 31, 1945, the same day.

GROSS PATHOLOGY. Autopsy was performed eight hours after death. The skin and sclerae were slightly jaundiced. There were numerous petechiae measuring from 0.5 to 1 mm. in diameter over the skin of the back, trunk and extremities. Several larger areas of ecchymosis from 4 to 6 cm. in diameter were present on the arms and legs. In the right superior cervical region were two healing abscesses covered with hard crusts. Healing superficial ulcerations were present in the skin around the anus and over both buttocks.

Heart: The heart weighed 420 Gm., was slightly enlarged but was otherwise not abnormal.

Lungs: The right lung weighed 725 Gm. The lower one-third was edematous and congested. There were numerous focal areas of hemorrhage, the largest measuring about 2 cm. in diameter. These were scattered throughout the upper and lower lobes but were more numerous in the lower lobe. The left lung was similar to the right.

Spleen: The spleen weighed 250 Gm. and was very soft in consistency.

Gastrointestinal Tract: This tract was entirely normal except for the rectum. In the rectum just proximal to the internal sphincter was a large, sloughing ulcer, 7.5 by 7 cm., with a well defined, punched out border and a dirty grayish-green base. The wall of the rectum adjacent to the ulcer was firm and markedly thickened; it measured 1.4 cm. in thickness.

Kidneys: The right kidney weighed 280 Gm. At the lower pole large soft adherent thrombi distended the branches of the renal vein. These had the appearance of antemortem thrombi. The left kidney weighed 300 Gm. Antemortem thrombi similar to those seen on the right were observed.

Bladder: The mucosa of the bladder was gray and trabeculated and exhibited congestion with several small areas of hemorrhage.

Bone Marrow: The femoral marrow was slightly redder than normal. The vertebral marrow was reddish-gray in color and the sternal marrow similar.

MICROSCOPIC. *Rectal Ulcer:* There was extensive degeneration and necrosis throughout the mucosa and submucosa and pronounced infiltration of all coats by lymphoid cells and large mononuclear leukocytes. A fibrino-hemorrhagic membrane covered portions of the necrotic mucosa. The ulceration had extended down through the submucosa and into the muscular coat. In the inner muscular coat there were large areas where the smooth muscle bundles were undergoing degenerative change and were heavily infiltrated with inflammatory cells composed of lymphocytes, plasma cells and large mononuclear leukocytes. There were no polymorphonuclear leukocytes and no definite leukemic cells in the exudate. In the outer muscular coat and serosa there were moderate chronic inflammatory cell infiltration and areas of fibroblastic proliferation. Numerous colonies of bacteria, mostly bacilli, were frequently seen in the necrotic tissue and within engorged blood vessels of the mucosa and submucosa. There was also proliferation of bacilli within the walls

of some of the vessels in the areas of necrosis. In the submucosa there was one large vein which was distended by a recent antemortem thrombus, a portion of which was adherent to the endothelial lining. Beginning fibroblastic organization was noted in one small area. There were colonies of bacteria within the thrombus and within the degenerated vessel walls.

Lungs: The blood vessels throughout the lung were markedly congested. A large irregular patchy area of acute bronchitis and bronchopneumonia was found. The exudate in this area was composed chiefly of masses of erythrocytes and fibrin and very few leukocytic cells, these consisting chiefly of lymphoid cells and a few macrophages. There were numerous bacilli in the bronchioles and alveolar spaces.

Spleen: There were areas of intense congestion and diffuse hemorrhage. There was a moderate number of large hyperchromatic cells with varying texture and staining reactions which appeared to be lymphoblasts. No foci or erythropoiesis or myelopoiesis were noted. No organisms were seen.

Bone Marrow: Focal areas of lymphocytic infiltration mixed with plasma cells and lymphoblasts were present. Cells of the myelopoietic series were very few in number and myelopoiesis is markedly reduced.

Hemolymph Nodes: The architecture was well preserved and the capsule was normal. There were occasional large basophilic cells with rare mitoses suggestive of lymphoblasts in the lymph cords and the sinuses.

Changes in the other organs were not striking. In the *kidneys* there was generalized edema, congestion and degenerative changes which accompany benign arteriolar nephrosclerosis. The *prostate* contained an area of infarction. No thrombosed vessels or leukemic infiltrations were seen. In the *liver* congestion and slight edema occurred with slight fatty infiltration and granular disintegration of the cytoplasm of the liver cells.

Bacteriology: Specimens taken from the lungs, liver, spleen and bone marrow grew B. pyocyaneus in pure culture. Culture of the healing abscess of the skin of the neck showed predominantly hemolytic staphylococcus aureus and a few colonies of B. pyocyaneus.

Final Diagnoses: (1) Aleukemic lymphatic leukemia; (2) B. pyocyaneus sepsis with ulceration of the rectum, and (3) terminal acute bronchitis and hemorrhagic bronchopneumonia.

Case iv. This patient had undergone multiple operations on the biliary tract. She suffered with wound infections, suppurative cholangitis, liver abscess and repeated bacteremias due to either B. coli or B. pyocyaneus. Treatment with sulfonamides and streptomycin was not curative, and sudden death occurred during B. pyocyaneus bacteremia. (Fig. 4.)

E. D. was a sixty-nine-year-old, white female admitted to the surgical service on January 23, 1946, complaining of right epigastic pain.

In September, 1945, a subtotal thyroidectomy was done for toxic adenomatous goiter, with uneventful recovery and relief of symptoms. There were no other significant illnesses in the past.

Her present illness began with right epigastric pain, sharp and intermittent in character, radiating through to the right scapula, produced by eating fatty or fried foods particularly, about nine months prior to admission. At this time a large, radio-opaque, laminated gallstone was visualized by *x*-ray. She had never had vomiting, jaundice, bloody or clay-colored stools, chills or fever. Because of persistence of symptoms she entered for operation with a diagnosis of cholelithiasis and chronic cholecystitis.

She was a thin, elderly woman in some discomfort but not severely ill. Temperature, pulse and respiration were normal. There was moderate peripheral arteriosclerosis. There was pronounced tenderness in the right upper quadrant of the abdomen but no other abnormalities. The liver and spleen were not palpable.

On admission, urinalysis was entirely normal. Hemoglobin was 13 Gm. per cent. White blood count was 6,200 per c.mm., with 80 per cent polymorphonuclear forms, 17 per cent lymphocytes, 2 per cent monocytes and 1 per cent eosinophiles.

On the second hospital day a cholecystectomy was done. The gallbladder was shrunken and fibrotic and contained a single large stone. At this time what was thought to be a diverticulum of the gallbladder was also removed. Her postoperative course was marked by increasing

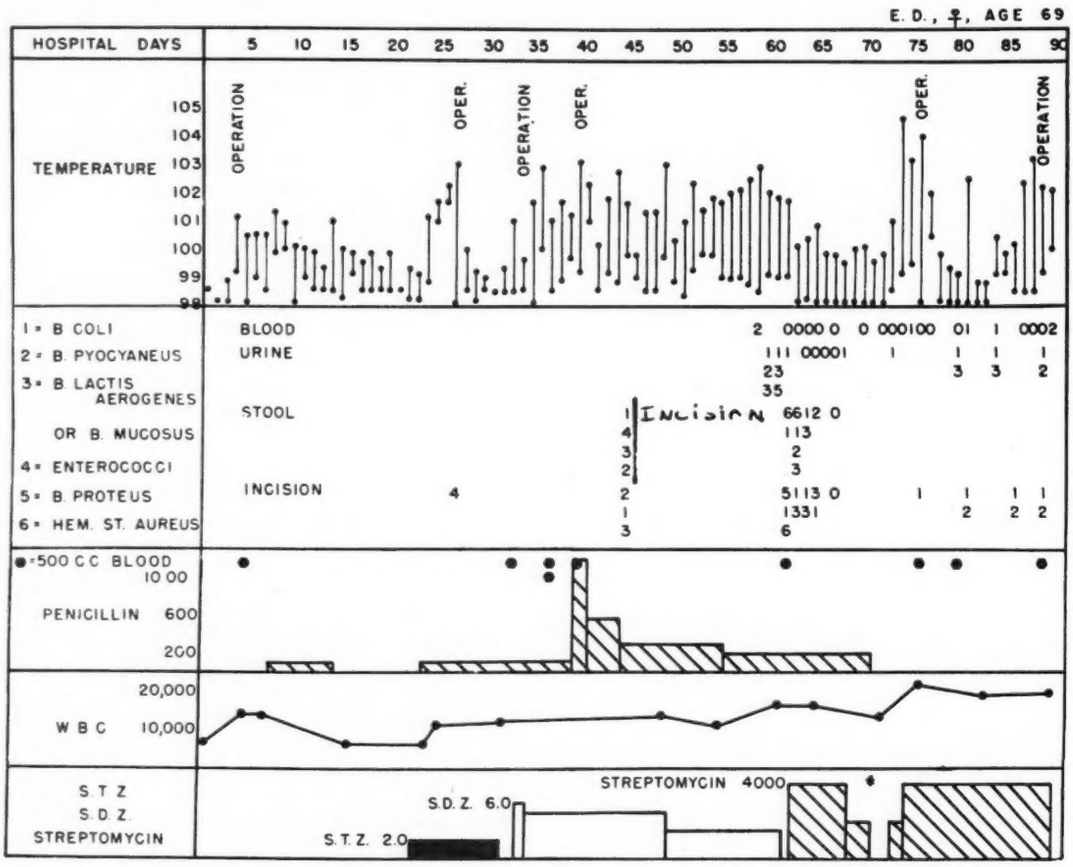

FIG. 4. Case IV. Fatal sepsis (B. coli and B. pyocyaneus) with suppurative cholangitis and liver abscess following multiple operations on the biliary tract.

icterus. There was a low-grade fever, which, however, rapidly increased to 103°F. from the fifteenth to the eighteenth hospital day. On the seventeenth hospital day, drainage of bile through a sinus in the incision site occurred. At this time exploration of the sinus tract was performed. A moderate amount of purulent bile was found and the area was drained. The temperature returned to normal. However, there was no improvement in the icterus, so on the thirty-third hospital day an exploratory operation was performed, and the common bile duct was anastomosed to the jejunum by means of a vitallium tube. Six days later the abdominal incision was resutured because of partial dehiscence. Although the jaundice diminished satisfactorily, her postoperative course was septic, with chills and daily fever, as high as 102 to 103°F., despite the administration of penicillin and sulfadiazine. Culture of the wound secretions on the forty-eighth hospital day revealed B. pyocyaneus predominantly and B. coli. On the fifty-ninth hospital day a blood culture revealed B. pyocyaneus. During the next two days cultures of the urine and of the abdominal wounds showed a mixed flora, with B. coli and B. pyocyaneus predominating. From the sixty-second to seventy-first hospital days, a total of 29 million units of streptomycin was given over a period of nine days in intramuscular injections every three hours. During this time the temperature returned to normal, the urine was sterilized, and the abdominal incisions healed.

However, within forty-eight hours after discontinuance of the streptomycin, fever reappeared, with chills associated with a B. coli bacteremia on the seventy-fifth day. Streptomycin was begun again on the seventy-fourth hospital day and continued until death, in doses of four million units daily. On the seventy-fifth hospital day, pronounced tenderness developed in the left upper quadrant. There was elevation of the left diaphragm and impairment

of motion. An exploratory incision was made and a small left subphrenic abscess, apparently originating in and communicating with the left lobe of the liver, was drained. B. coli in pure culture was grown from the pus. Her temperature diminished rapidly, but soon intermittent chills and fever again appeared, with B. coli bacteremia on two occasions during the next thirteen days. Cultures of the urine and of the left upper quadrant incision showed B. coli and B. pyocyaneus.

Because of continued septic course, with *x*-ray evidence of elevation of the right diaphragm, an exploration of the right subphrenic region was carried out through a posterior incision on the eighty-ninth hospital day. No evidence of a subphrenic abscess on the right was found. On the afternoon of the ninetieth day she experienced another shaking chill. While the blood was being drawn for culture, she died suddenly. B. pyocyaneus was grown from this terminal blood culture.

GROSS PATHOLOGY. The body was emaciated. There were no significant skin lesions present. The parietal peritoneum over the right upper quadrant was slate black in color and shaggy. There were many adhesions between the viscera and the anterior abdominal wall, particularly at the incisional sites.

Spleen: The spleen weighed 365 Gm. The pulp was very mushy and soft, and the follicles were less prominent than normal.

Liver: The liver was normal in size. The choledocho-jejunostomy was patent and functioning, although the area of the liver to which the jejunum was anchored was necrotic and gray in color. On the superior surface and anterolateral margin of the left lobe there was a ragged cavity 2 cm. deep and 3 cm. in diameter, lined by necrotic tissue and containing thick, gray pus. The abscess was surrounded by adhesions and communicated with the left subcostal incision by a sinus tract. The cut surface of the liver was brownish-yellow and presented a nutmeg appearance. Pinhead-sized and larger drops of yellow purulent material could be expressed from the radicles of the biliary tract.

Kidneys: The right kidney weighed 170 Gm. and the left 160 Gm. On cut surface the pallor was marked. The cortices were 3 mm. thick. The capsules stripped easily and revealed finely granular surfaces. The left pelvis and ureter were normal. There was a double pelvis and ureter on the right. The pelvis and ureters of the right kidney were slightly injected and contained yellow pus. The perirenal fat on the right was thickened and edematous.

Urinary Bladder and Urethra: The mucosa of the urinary bladder and urethra was markedly hemorrhagic and edematous. The vesicle contained thick, yellow pus.

Gastrointestinal Tract Pancreas and Adrenals: These organs were normal.

Heart: The heart was normal except for a moderate degree of atheromatosis of the coronary arteries.

Lungs: The lungs were normal except for complete atelectasis of the lower half of the right lower lobe. There were no infarcts, antemortem thrombi or emboli.

Trachea and Bronchi: The trachea and bronchi were essentially normal. There were no antemortem thrombi discovered after complete dissection of the tributaries of the inferior vena cava.

MICROSCOPIC PATHOLOGY. *Liver:* There was patchy disorganization of the lobules with intervening fairly normal areas. In the latter the liver cords were widely separated by markedly dilated sinuses packed with red blood cells. The lumens of some of the bile ducts were filled with polymorphonuclear leukocytes, and there was an increase in the periportal connective tissue. In some areas necrosis of the lobules had occurred with fibrous replacement; the connective tissue contained scattered lymphocytes and an occasional necrotic liver cell. One section through the main intrahepatic ducts showed necrosis of the liver lobules and tremendous periductal fibrosis with lymphocytic infiltration. The epithelium of the ducts was completely desquamated. The wall of the abscess in the left lobe consisted of fibrin, polymorphonuclear leukocytes, large mononuclear leukocytes and a few necrotic liver cells. This fibrino-purulent exudate contained several small scattered groups of bacilli. The liver capsule in this area was thickened, fibrotic and infiltrated with lymphocytes, large mononuclear leukocytes and a few polymorphonuclear leukocytes.

Spleen: There was some hyalinization of the walls of the arterioles. The sinuses were engorged with red blood cells, polymorphonuclear leukocytes and a few large mononuclear leukocytes. In one section there was marked congestion of the pulp with diffuse hemorrhage and intensive polymorphonuclear infiltration. No organisms were seen.

Kidneys: There was a patchy distribution of inflammatory and degenerative changes. Beneath the capsule roughly triangular areas of lymphocytic infiltration occurred. There was hyalinization of the basement membrane of the glomeruli near these areas; some glomeruli were completely hyalinized. In some glomeruli a few scattered polymorphonuclear leukocytes were found. The capsular spaces contained deposits of granular material. The convoluted tubules were lined by deeply eosinophilic staining cells, some of which were vacuolated and some were desquamated. Most of the tubules contained albuminous deposits and a few desquamated epithelial cells. In the lumens of the collecting tubules were basophilic staining casts. The blood vessels were thickened and showed intimal fibrosis with occasional reduplication of the internal elastic lamina. No organisms were seen.

Bladder: In some areas the epithelium of the mucosa was desquamated. There was marked edema of the submucosa. The cells were widely separated and heavily infiltrated by lymphocytes, plasma cells and large mononuclear leukocytes. There were numerous hugely dilated, engorged, thin-walled blood vessels in the submucosa.

Lungs: The pleura was thickened and fibrotic with numerous foci of lymphocytes and large mononuclear leukocytes. There was intimal fibrosis of the blood vessels in the fibrotic areas.

The other organs were not significantly abnormal, except for slight atherosclerosis of the coronary arteries and the aorta. No vascular lesions characteristic of B. pyocyaneus septicemia could be found.

Cultures from the peritoneal cavity near the hilum of the liver showed B. coli, B. pyocyaneus. Cultures from the liver revealed B. coli, B. pyocyaneus, B. mucosus capsulatus, and cultures from the spleen showed no growth.

Final Pathological Diagnoses: Acute and chronic suppurative cholangitis—B. coli and B. pyocyaneus; liver abscess with sinus to anterior abdominal wall—B. coli originally; secondarily infected with B. pyocyaneus; biliary cirrhosis (infectious) slight; localized peritonitis with adhesions—B. coli and B. pyocyaneus; chronic pyelonephritis; chronic cystitis; pulmonary atelectasis, right lower lobe, and coronary and aortic atherosclerosis, slight.

INVOLVEMENT OF THE SKIN AND APPENDAGES

The skin is the most frequently involved organ in local as well as systemic infections.[2] This would be expected from the common location of the organisms in moist areas of the normal skin in the axillary and anovulval regions particularly in people who bathe infrequently.

Local Infections. In its rôle as an ubiquitous secondary invader B. pyocyaneus often contaminates surgical wounds especially those in the abdomen and perineum. Its presence can be recognized by the characteristic blue-green pus produced. The organism was first isolated in pure culture by Gessard[1] in 1882 from such situations. Slowly healing indolent ulcers such as varicose and thrombophlebitic ulcers and chronically draining sinuses from tuberculous and pyogenic osteomyelitic foci are commonly secondarily infected with the B. pyocyaneus. Invasion of untreated decubitus ulcers in the sacral region almost always occurs (Case 1).

Mallannah[30] reported the case of an Indian with several perforating ulcers of the foot which with several other features so resembled leprosy that specific treatment had been given, but without benefit. No lepra bacilli were identifiable in the scrapings, but there were many gram-negative bacilli which proved to be B. pyocyaneus on culture. The duration of the illness was one year; recovery occurred after treatment with autogenous vaccine for eight weeks.

Kopetzky and Almour[31] described five cases of an erysipelas-like cellulitis of the

skin which spread from mastoid wounds. In one case the mastoiditis was apparently primarily due to this organism while in the others the wounds were secondarily infected after operation. No hemolytic streptococci were culturable from the wounds at the time of the spreading skin infection. The cellulitis involved the scalp, face and neck, and in one instance gangrene of the subcutaneous tissue of both eyelids was produced.

Goldman and Fox[32] described two cases of infection of the skin surrounding the fingernails with development of a brilliant green discoloration of the nails which persisted after subsidence of the paronychia. The soluble green pigment had apparently penetrated the nails without actual infection of the latter.

Cutaneous Manifestations of Systemic Infections. Prominent among the signs of pyocyaneus sepsis are skin lesions which begin as macules or vesicles and later become bullous and often pustular. When the surface epithelium is denuded from these latter and the center sloughs out a characteristic ulcerating gangrenous lesion is produced. This was first described by Barker[34] in 1897 and was later called "ecthyma gangrenosum" by Hitschmann and Kreibich.[25] Detailed descriptions of ecthyma of this type were given by Fraenkel[2] in his classic paper in 1917. It is most commonly encountered in the ano-genital region, also in the axillae, inner aspects of the thighs and the abdomen, particularly in children. The organism is easily cultured in abundance from these areas of gangrenous skin. The necrosis may penetrate through the skin and subcutaneous tissue to the underlying muscle. Fraenkel considered that the pathognomonic histologic picture was the finding of thick collections of slender gram-negative rods in the vessel walls of a lesion, particularly in the media and adventitial layers. Sometimes there was a panarteritis with arterial thrombosis. The pathogenesis of such lesions is apparently the result of two factors, actual cutaneous infarction through mechanical plugging of the vessels because of multiplication of bacilli in their walls, as well as the action of a proteolytic enzyme produced locally by the large numbers of organisms.

Other lesions of the skin seen during the course of bacteremia include the roseola which resembled rose spots occurring in cases of "Shanghai fever" described by Dold.[15,16] This entity closely simulated typhoid fever except for its short duration. B. pyocyaneus could be cultured from the cutaneous lesions, but they spontaneously involuted and never progressed to ecthyma.

The report of Guy and Cohen[33] concerns the development of typical generalized exfoliative dermatitis of the newborn (Ritter's disease) in a premature infant. At autopsy on the ninth day was found acute pericarditis, pleuritis and peritonitis all due to B. pyocyaneus, and shallow ulcers throughout the small intestine. B. pyocyaneus was also cultured from the heart blood. It is quite likely that the sepsis in this baby had its origin in infection of the umbilicus.

Erythema nodosum,[35,36] erythema multiforme and butterfly lesions of the face[26] resembling lupus erythematosus have also been described during the course of systemic infections with B. pyocyaneus. The relationship of these manifestations to the disease is not clear as no cultures or microscopic examinations were carried out.

INVOLVEMENT OF THE GASTROINTESTINAL TRACT

Next to the skin the alimentary tract is the most frequently invaded part of the body. Any portion may be involved from the lips, mouth and pharynx to the rectum and anus.[2,23,26,34,37] There is now adequate evidence[37] that the lesions of the stomach and intestines at least can be either primary,

resulting from local invasion from organisms in the lumen, or secondary to bacteremia and hence analogous to the skin lesions ecthyma gangrenosum.

In general, the pathologic lesions consist of circumscribed 2 to 12 mm. areas of necrosis of the surface epithelium which appear grossly as ulcers with the bases covered with yellow crusts. In the tonsil the necrosis may produce deep cavities which extend to include the capsule and even penetrate into the surrounding muscle.[2,37] In the ileum the ulcerations involve not only the Peyer's patches but also the adjacent mucosa and usually lie opposite the attachment of the mesentery.[37] Confluence of these ulcerations may result in the involvement of large areas of the small intestine[34] or the stomach.[2] On section extension into the submucosal layer is often seen. Large masses of bacilli are found in the necrotic bases and margins of the ulcers (Cases I and III). The blood vessels in the periphery of the lesions are often thrombosed and characteristically show infiltration with large numbers of organisms especially in the media and adventitia and in the perivascular spaces. Suppurative mesenteric adenitis with a pure culture of B. pyocyaneus from the involved glands was described by Barker,[34] although this is rare; hyperemia without other change is the usual finding. Gangrene of the anorectal region with extension into the ischiorectal fossa and involvement of the overlying skin has been noted.[26]

The clinical picture varies considerably. Infants and young children[2,38,39] are specially apt to be afflicted. On the lips and soft palate the lesions may be punctate and resemble "aphthous" ulcers. At the other extreme the necrosis of the tonsil and pharyngeal mucous membrane may be so great as to simulate severe scarlet fever or diphtheria.[2,23,24,27]

Epidemics of diarrhea of the newborn with high mortality have been ascribed to this agent. In children and adults an acute or subacute enteritis with diarrhea alternating with constipation and with or without significant constitutional symptoms may occur.[2,38,39,40] However, on occasion the disease may assume the picture of typhoid fever[15,16] with prostration, headache, high fever, roseola from which the organisms can be recovered, splenomegaly and bacteremia in addition to the gastrointestinal manifestations. Some of these cases have been characterized by Dold as "Shanghai fever" or "13-day fever" because of their short duration. This similarity to typhoid is heightened by the frequent finding of B. pyocyaneus in the bile and in the gallbladder at autopsy and operation, and in experimental animals with induced bacteremia.[35,37] None of the catastrophic complications of typhoid, as massive hemorrhage into the gastrointestinal tract or perforation of the gut with peritonitis, has been reported, although the case of peritonitis[34] is suggestive.

The diarrheal stools have been noted to be greenish, mixed with mucus and blood-streaked. There is no mention of purulent stools in the literature. Culture may yield a striking abundance of B. pyocyaneus; at times as high as 50 to 75 per cent of the colonies are those of this organism.

In this connection, it may be noted that the finding of B. pyocyaneus in routine stool cultures is not common and the number of organisms is small; positive cultures vary from 13 out of 3,000[12] to 2.5 per cent of 124.[11] In the latter group the cultures were made in an area where contamination of the drinking water with this organism was frequent.

In diagnosis obviously reliance must be placed mainly on recovery of the organisms from the local lesions, stools or blood. If ecthyma gangrenosum is present, additional strong evidence is adduced as to the causative rôle of the B. pyocyaneus. A rising titer

of agglutinins against the patient's own organism may afford further necessary evidence when the only bacteriologic finding in a case of enteritis is a positive stool culture.

INFECTIONS OF THE URINARY TRACT

In the overwhelming majority of instances the finding of B. pyocyaneus in the urine together with other evidences of infection indicates that there has been previous manipulation, either catheterization, cystoscopy, or bladder or kidney surgery, with introduction of the organisms in this manner.[42,47] The frequent presence of the organism on the skin of the ano-genital region is a factor which makes such implantation relatively easy especially in females. These infections are frequently mixed, with several varieties of gram-negative bacilli in the urine, usually including B. coli.

In adults one of the commonest portals of entry of this organism is by way of the urinary tract. Bacteremia is the common cause of "catheter chills"; occasionally B. pyocyaneus is the organism cultured from the blood (four of eighty-two patients with positive blood cultures—Scott;[42] one of sixty-four patients with positive blood cultures—Hyman and Edelman.[43] Other instances of bacteremia following instrumentation have been reported by Barrington and Wright[44] and by Ewell[45] and with secondary localization elsewhere by Scheim[110] (thoracic vertebrae), Moragues and Anderson,[50] Fish et al.[48] (endocarditis) and Kline and Maschke[26] (lung).

Most frequently in ascending infection cystitis alone is produced. When involvement of the bladder mucosa is superficial, with hyperemia and edema only as is usually the case, the prognosis is relatively good though bacilluria may persist for some weeks and recur following cessation of therapy. Obviously other factors such as obstruction with presence of residual urine may be more important here than the type of infecting organism. On rare occasions the mucosal lesions may assume a necrotic character similar to those encountered in involvement of the gastrointestinal tract.[34] Our Case 1 is an extreme example of this type of cystitis, with extension of the necrosis of the mucous membrane to the ureter and kidney pelvis.

Prostatitis with abscess formation has been described twice.[48,50] Curiously enough dissemination from these foci resulted in endocarditis in both cases. There was thrombosis of the periprostatic veins in one case.

Extension to the kidney with abscess formation throughout is rare and appears to present a histological picture similar to ascending pyelonephritis of equal severity caused by other organisms such as B. coli (Case 1).[46,26] In Fraenkel's case,[2] however, the cellular infiltration of the lesions was almost entirely mononuclear, in contrast to the predominantly polymorphonuclear character of the exudate described by Kline and Maschke and Roedelius, and in our case.

In contrast to the picture in ascending pyelonephritis is that seen in the kidney in sepsis.[2,46] During the latter the tendency to vascular inflammation is commonly manifested in the kidney with infiltration of arteriolar and arterial walls with bacilli, thrombus formation and production of infarcts. These areas of anemic necrosis do not break down and suppurate. Areas of focal glomerulonephritis have been noted in only one case, that of a patient with acute endocarditis.[50]

B. pyocyaneus does not split urea to form ammonia. No tendency to stone formation is associated with B. pyocyaneus urinary tract infection. Only one report concerns this subject:[46] Following removal of an aseptic calcium oxalate stone from the

kidney pelvis a unilateral pyelonephritis developed which was refractory to treatment. One year after the first operation the kidney was removed after formation of a second stone, this time composed of calcium phosphate; from the center of this calculus B. pyocyaneus was cultured.

CASE V. In this case there was benign prostatic hypertrophy with bladder neck obstruction and cystitis and pyelonephritis due to B. coli, B. pyocyaneus and B. mucosus. Infection by all organisms persisted following operation and treatment with sulfathiazole (penicillin) and streptomycin.

E. H. was a sixty-four-year-old male who complained of frequency and nocturia. During the two years before admission, there was a progressive decrease in the size of the urinary stream, nocturia two times per night and day frequency. During the week before admission, there was diarrhea with slight fever, lower abdominal cramps and partial urinary retention with constant dribbling.

The temperature was normal and the chest was emphysematous. There were bilateral large direct inguinal hernias. The bladder was distended half-way to the umbilicus. No costovertebral angle tenderness was present. There was three plus prostatic enlargement with a nodule in the left lobe.

Laboratory examination revealed the following: Urine: Specific gravity 1.024; no albumin or sugar; and many leukocytes and erythrocytes in the sediment. Culture revealed B. coli, B. pyocyaneus and B. mucosus, 95,200,000 per cc. before streptomycin was started. Non-protein nitrogen was 43 mg. per cent. Intravenous pyelogram: Both kidneys were normal in size, shape and position. There was a minimal degree of dilatation of the renal pelves and calyces of both kidneys, more marked on the right. The pelvic portions of both ureters were dilated and remained filled. There was trabeculation of the bladder. The base of the bladder was elevated due to prostatic enlargement.

After four days of sulfathiazole therapy (1.5 Gm. daily) at the hospital a suprapubic prostatectomy was performed. During the fifteen days after operation there was a low-grade fever, as high as 100.6°F. Sulfathiazole was continued and penicillin, 120,000 units per day, was given. On the twenty-second hospital day, after the above findings indicated a persistent infection, penicillin and sulfathiazole were discontinued, and streptomycin, 1 Gm. daily, was administered for a total of 9.5 Gm. The streptomycin likewise failed to sterilize the urine, but the slightly elevated temperature returned to normal during its administration, where it remained during the remainder of the hospital course.

CASE VI. In this case bladder calculus with cystitis and left pyelonephritis due to B. pyocyaneus, B. coli, B. proteus and B. mucosus were present. After operation and streptomycin treatment all organisms were eliminated from the urine except B. coli, which persisted in increased numbers.

N. S. was a seventy-two-year-old male whose chief complaints were suprapubic and low back pain and dysuria. Following suprapubic prostatectomy several years ago for benign prostatic hypertrophy, he had been asymptomatic. Five months before admission pain on urination in the perineal and suprapubic regions, low backache and nocturia five to six times a night had begun and continued until admission. *X*-ray examination revealed a bladder stone.

His temperature was normal and blood pressure was 140/60. There was generalized arteriosclerosis of a moderate degree and a right direct inguinal hernia. There was moderate tenderness in the left costovertebral angle and flank. The prostate was firm, slightly enlarged symmetrically and slightly tender.

Laboratory examination revealed the following: Urine: albumin 2+; sugar negative. Microscopic examination: many leukocytes and erythrocytes in the uncentrifuged specimen. Non-protein nitrogen was 41 mg. per cent. Hemogram was normal. Urine culture before treatment revealed B. pyocyaneus, B. coli, B. proteus and B. mucosus, 28,000,000 per cc.

On the third hospital day, a suprapubic cystotomy and removal of the calculus was performed. On the day following operation, streptomycin, 0.25 Gm. every six hours intramuscularly (1 Gm. daily), was begun and continued for a total of 5.75 Gm. The urine was sterilized of the other organisms except B. coli, which was pres-

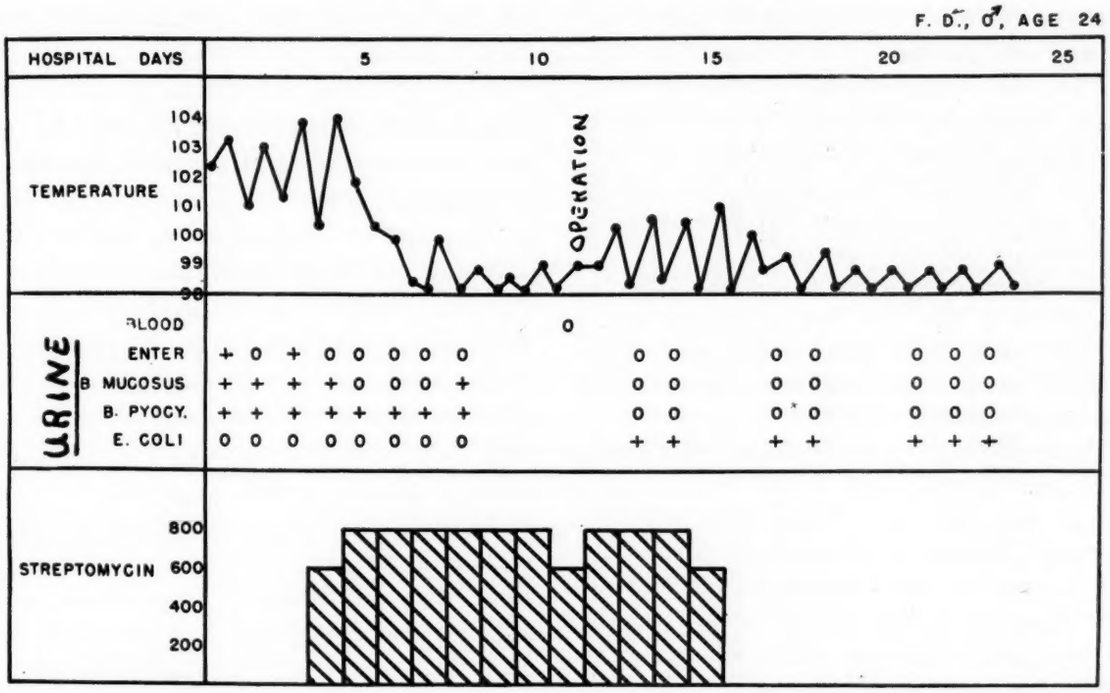

FIG. 5. Case VIII. Development of persistent bacilluria due to a different, resistant organism after operation and streptomycin treatment had apparently cured a mixed urinary infection.

ent in increased numbers (148,000,000 per cc.) on discharge.

CASE VII. Benign prostatic hypertrophy with bladder neck obstruction and cystitis were present due to B. coli, B. pyocyaneus, and B. mucosus. Operation and treatment with streptomycin were carried out followed by sterilization of the urine of the latter two organisms but persistence of the B. coli infection.

J. L. was a sixty-seven-year-old male whose chief complaint was nocturia and dysuria of three years' duration. For the fifteen years before admission slight urinary frequency and nocturia had been present and had gradually progressed. On admission there was nocturia five to six times, with slight pain at the beginning of urination, difficulty in starting urination, small stream and terminal dribbling. There had been no retention.

Upon admission his temperature was 98.6°F. The only significant abnormal finding was a prostate which was enlarged to two times normal size but non-nodular and symmetrical.

Laboratory examination revealed the following: Urine: albumin, slightest possible trace; sugar, negative; occasional leukocytes, no erythrocytes or casts. Urine culture: B. coli, B. mucosus, and B. pyocyaneus. Blood: normal. Non-protein nitrogen 36 mg. per cent.

On the fourth hospital day, a transurethral prostatectomy was performed following which streptomycin, 0.25 Gm. every six hours intramuscularly, was started. An uneventful postoperative course ensued except for a febrile rise on the fourth day after operation which may have been due to the removal of the Foley catheter or to the streptomycin. The streptomycin was discontinued on the fourth day; following this, the temperature promptly returned to normal. During the course of therapy, the B. pyocyaneus and B. mucosus disappeared from the urine, although B. coli was still present on discharge on the eleventh hospital day.

CASE VIII. Mixed urinary infection due to B. pyocyaneus, enterococcus and B. mucosus developed after instrumentation in a patient with renal lithiasis. These organisms disappeared after treatment with streptomycin and nephrectomy, but a strain of B. coli appeared then which resisted further therapy. (Fig. 5.)

F. D. was a twenty-four-year-old male who had been discharged from this hospital three days before after studies, including cystoscopy and retrograde pyelography, had revealed a

large stone in the left kidney. Nephrectomy had been advised. During the intervening three days he had had fever, ranging between 101 and 103°F., malaise, vomiting and passage of mucus and pus in the urine. There had been no back pain or chills. He had been given 2 Gm. of sulfa drug and 30,000 units of penicillin during the twelve hours before entry.

Physical examination revealed the temperature to be 102°F. The only other significant findings were slight dehydration and slight bilateral costovertebral angle tenderness. The prostate was normal.

The hemogram was normal, with white blood count 6,550 per c. mm. Non-protein nitrogen was 23 mg. per cent. Urine cultures before treatment showed B. pyocyaneus, enterococci and B. mucosus. After treatment and operation, these organisms disappeared but B. coli appeared and persisted in the urine until discharge.

The patient's temperature remained elevated, 101 to 103°F., during the first five hospital days, but fell rapidly to normal after institution of streptomycin therapy, 0.2 Gm. intramuscularly every six hours, on the fourth day. This was continued for eleven days, including four days after operation, for a total of 9 Gm. On the eleventh hospital day a left nephrectomy was performed. The course following operation was uneventful, there being a low-grade fever, as high as 101°F., during the first five postoperative days. He was discharged with the persistent B. coli bacilluria to be further treated as an out-patient.

ENDOCARDITIS

Endocarditis due to the Bacillus pyocyaneus is one of the rarest manifestations of infection with this organism. The literature was reviewed by Fish, Hand and Keim[48] in 1937 at which time a case of their own was added. Since that time Kearns[49] and Moragues and Anderson[50] have reported cases. This brings the total number of previously reported cases to eight, at least one[51] of which is of doubtful validity. Because of their rarity the cases described in the literature are summarized briefly below. To this total we add a somewhat unusual case (Case IX).

Barker[34] (1897) reported the first case, that of a forty-one-year-old woman who had had diarrhea, vomiting and anorexia, asthenia and swelling of the right leg of three or four weeks' duration. The patient was pale and emaciated with tense protuberant abdomen, saphenous thrombophlebitis and beginning sacral decubitus. At autopsy on the seventh day a vegetative mitral endocarditis, extensive ulceration of the small and large intestine with acute peritonitis, chronic pelvic cellulitis, peritonitis with ovarian abscess and a recto-vaginal fistula were found. There were also cancer of the stomach, old pulmonary tuberculosis, acute and chronic bronchitis with bronchiectasis and fibrino-purulent pleurisy and a double hydronephrosis with amyloid disease of the kidneys. Cultures from the mitral vegetations, peritoneum, intestinal ulcers, and ovarian abscesses showed pure growths of B. pyocyaneus. The portal of entry here apparently was the gastrointestinal tract. (This is the same case reported by Thayer[52] in 1926.)

Blum's[53] case (1899) was that of a baby boy two and one-half months old who also had congenital syphilis. It is not known by which route the organism gained entry to the blood stream. There was no apparent focus of infection; there were no blood cultures taken during life. At autopsy endocarditis of the mitral valve was found; many gram-negative bacilli were seen in the vegetations which proved to be B. pyocyaneus in pure culture.

De la Camp[54] (1904) described a fifty-one-year-old woman with a chronic illness of over a year's duration characterized by daily chills, fever, severe headache and numerous cutaneous abscesses which appeared intermittently during the course. On admission she was thin, icteric, had hepatomegaly and tremendous splenome-

galy. The heart was apparently normal. During the thirty-eight-day hospital course it was demonstrated that abscesses of the skin and external ear contained B. pyocyaneus. Vesicular and bullous skin lesions and others characteristic of ecthyma gangrenosum also appeared. At autopsy there were five warty, hard, light grey-red, firmly adherent vegetations on the free margins of the mitral valve. Also present were caries of the right petrous bone, recent infarcts of the spleen, saccular aneurysm of the splenic artery (? mycotic) and ulcerations of the nasal mucous membrane. B. pyocyaneus was cultured from the heart's blood in pure culture and with staphylococcus from the scrapings of the mitral vegetations and from the spleen. The portal of entry was probably the skin, although this is not definite. B. pyocyaneus was not recovered from the blood during life.

Rolly[55] (1906) reported a case of a twenty-eight-year-old woman who died after an illness of eleven days' duration. Two months before her fatal illness she had had a period of fever and abdominal pain from which, however, she recovered in ten days. She was treated for typhoid fever because she was living in a house where there were several other cases of typhoid, although there were no typical manifestations of the disease in the patient and a prompt recovery was made. Her course was characterized by septic temperature, many hemorrhagic skin emboli, splenomegaly and meningitis with terminal bronchopneumonia. B. pyocyaneus was repeatedly demonstrated in the blood and in the spinal fluid. At autopsy there was found to be purulent meningitis, vegetative endocarditis implanted on an old mitral valvular lesion, metastatic abscesses in the spleen and kidneys, enlarged uterus with partially retained placenta, corpus luteum of pregnancy and confluent lobular pneumonia. B. pyocyaneus was grown from the blood, meninges, mitral vegetations and various other organs. It was thought that the source of entry of the organism was the uterus.

Kearns'[44] (1936) case was that of a thirty-five-year-old heroin addict who complained of anorexia, weakness, fever, chilly sensations and painful swelling of the left forearm. On admission there was a temperature of 102°F., bilateral bronchopneumonia and an abscess on the dorsum of the left forearm. During a febrile downhill course of eighteen days' duration repeated cultures of his blood and urine yielded B. pyocyaneus alone. Postmortem revealed endocarditis of both the aortic and mitral valves and bilateral bronchopneumonia. The intima of the aorta in one location adjacent to the aortic valve was necrotic. There was focal endarteritis of the pulmonary artery a short distance above the pulmonic valve. Numerous slender bacilli in groups and short chains were demonstrated in all these lesions. No postmortem cultures were reported. The portal of entry was the skin abscess.

Fish, Hand and Keim[48] (1937) described a case of a seventy-one-year-old man with recurrent acute urinary retention which had necessitated repeated catheterizations. A suprapubic prostatectomy was done for benign prostatic hypertrophy. Sections of the excised prostate revealed focal suppurative prostatitis with abscesses. Later, on retrospective search, gram-negative bacilli were found in clusters around remnants of corpora amylacea in these abscesses. Between the seventh and twenty-seventh postoperative days there was a septic course, with six blood cultures positive for B. pyocyaneus during the last eight days. At autopsy on the twenty-seventh day postoperatively there was vegetative endocarditis of the aortic valve with the underlying valve necrotic and infiltrated with polymorphonuclear leukocytes. Within the vegetation were many colonies of gram-negative bacilli,

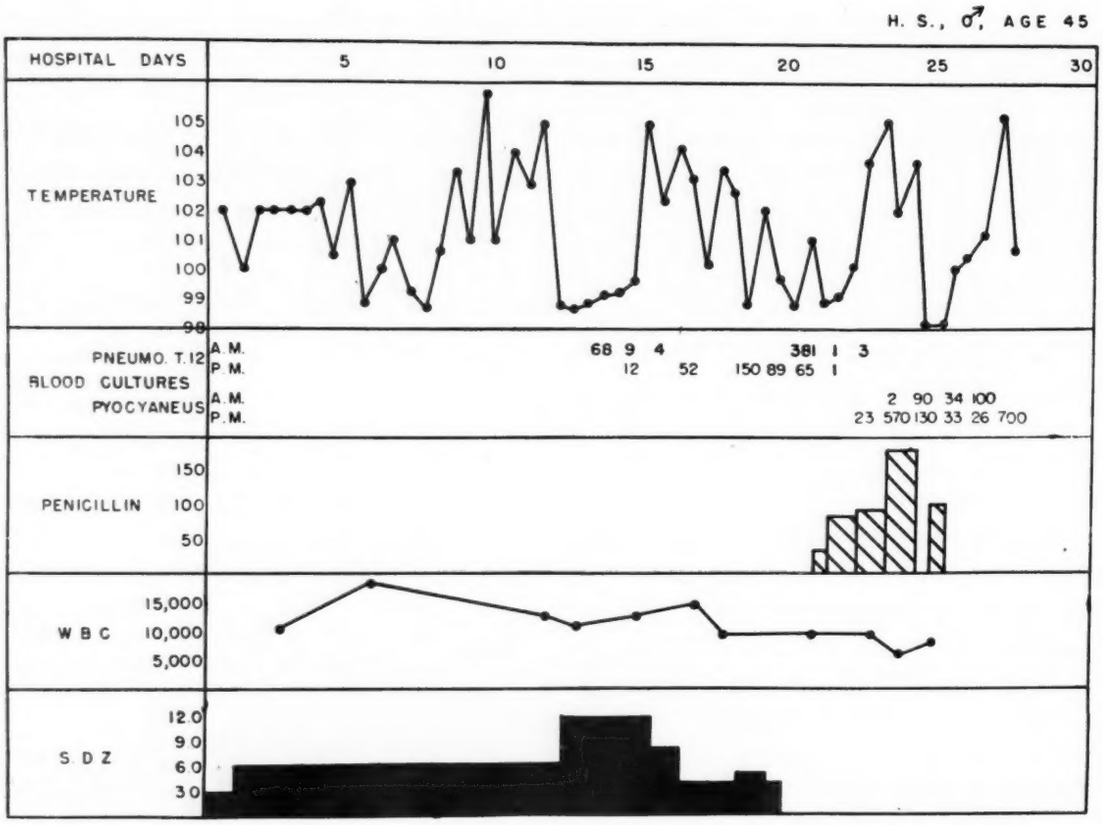

FIG. 6. Case IX. Pneumococcus endocarditis cured by penicillin treatment with death caused by superimposed pyocyaneus endocarditis.

In the aorta above the valve there were two large granular areas of acute bacterial aortitis with similar organism found in their interiors. There were focal necroses in the liver and kidneys. A branch of the renal artery was thrombosed and the wall infiltrated with polymorphonuclear leukocytes. The focus of infection was the prostate with inadvertent dissemination at the time of operation.

Moragues and Anderson[50] (1943) described a sixty-six-year-old diabetic man who had had symptoms of urinary obstruction for three months, dyspnea for two weeks and high fever, chills, headache and diarrhea for four days before admission. During his fifteen-day hospital course his temperature was septic and there were three blood cultures positive for B. pyocyaneus. On the ninth day he developed meningitis, with pleocytosis of the spinal fluid (567 cells per c. mm.) but with the fluid sterile on culture. At necropsy there was mitral stenosis with large friable grayish vegetations on the auricular surface of the valve. There was an abundance of small rod-shaped bacteria in the mitral vegetations which were identified culturally as B. pyocyaneus. This organism was also cultured from the meninges. There was infiltration of the meningeal blood vessels by acute inflammatory cells. There were areas of necrosis with abscess formation in the prostate, with bacteria demonstrable in these abscesses. There were areas of infarction and acute focal glomerular nephritis in the kidneys.

Bungeler[51] (1927) described the case of a sixty-five-year-old man who had rheumatic heart disease with mitral insufficiency and who died from sepsis following repeated intravenous injections of a mixture of live organisms among which were B. pyocyaneus

("saprovitan"). At necropsy endocarditis of the mitral valve with perforation was found, with multiple small abscesses in the kidneys and spleen. Postmortem blood culture from the femoral vein was sterile. From the spleen, B. proteus, B. pyocyaneus and cocci in chains were grown. There were no blood cultures taken during life, no cultures from the heart valves and no descriptions of microscopic sections of the vegetations. The characteristic blood vessel pathology of B. pyocyaneus infections was not found. There was no justification for the diagnosis in this case of B. pyocyaneus endocarditis on the evidence cited, although it is usually included in reviews of this subject.

CASE IX. This is a case of pneumococcic endocarditis cured by penicillin treatment. Tricuspid endocarditis due to B. pyocyaneus superimposed followed by death. (Fig. 6.)

H. S. was a forty-five-year-old, colored male who complained of pain and swelling of the right knee of three days' duration. For the week prior to admission he had been on a drinking bout. Three weeks prior to admission he had contracted a cold with a dry, non-productive cough, which had persisted for one week. No sore throat was noted.

The patient had had gonorrhea twenty-five years before. A similar episode of arthritis of the right knee of three days' duration had occurred two years prior to admission.

On admission his temperature was 102°F., pulse 140, respiration 26. The patient was acutely ill but in no great distress. Except for the above noted arthritis of the right knee, there were no significant abnormal findings. The heart was of normal size. There were no murmurs, thrills or abnormal pulsations. The lungs were clear and resonant.

Laboratory examination revealed the following: White blood count 10,000 per c. mm. with a predominance of polymorphonuclear leukocytes. With the exception of a white blood count of 18,000 per c. mm. on the sixth day, the range was between 7,000 to 14,000 throughout. There was no anemia. *X*-ray of the chest revealed an area of pneumonitis consistent with pneumonia in the right lower lobe. Two days later this area was wedge-shaped and appeared to be a healing infarct.

Blood cultures from the tenth to the twenty-second day revealed from 4 to 381 colonies of pneumococcus type XII. From the twenty-third to the twenty-eighth day (death) the blood contained from 23 to 700 colonies of B. pyocyaneus per cc.

In the hospital there were daily chills, with septic type of temperature curve, ranging from normal to 106°F. For the first nineteen days in the hospital he was treated with sulfadiazine in doses from 6 to 12 Gm. per day. When the pneumococcus bacteremia was discovered he was also given antipneumococcus (rabbit) serum, without apparent therapeutic effect. On the twenty-first day, penicillin was begun; over a period of four days a total of 480,000 units was given. The pneumococci disappeared from the blood stream within approximately twenty-four hours after penicillin therapy was begun. However, from the twenty-third day until death the blood stream contained B. pyocyaneus daily. He continued the septic course, went rapidly downhill and died on the twenty-eighth hospital day.

Pathology. A small vegetation was present on the tricuspid valve. Culture revealed only B. pyocyaneus (35 per Gm. of vegetation). There was a thrombus in the pulmonary artery to the right lower lobe, and an organizing infarct of the right lower lobe. The only organism cultured from the valve, thrombus and infarct was B. pyocyaneus. This finding was confirmed by two different laboratories.

(To be concluded in the next issue.)

Seminars on Rheumatic Fever

Rheumatic Heart Disease in the Adult*

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I was asked to describe rheumatic heart disease in the adult. This is very much like asking one to describe the entire subject of acquired heart disease, excluding arteriosclerotic and syphilitic heart disease. This task is altogether too big. I shall be content to make a few points that seem to be of reasonable importance.

Etiology. Much has been written and many opinions have been expressed regarding the cause of rheumatic disease. Some of these opinions have been dogmatic; others have been reasonable on the basis of knowledge. All of us have had the experience of observing a rheumatic attack following invasion of the upper respiratory tract by the hemolytic streptococcus. Some are convinced that this type of infection acts as a trigger mechanism for reactivation of the rheumatic process in the susceptible individual. Frankly, I do not think that this has been proven. On the basis of such a concept, some have claimed that if one could prevent invasion of the upper respiratory tract by the hemolytic streptococcus, further rheumatic damage to the heart might be prevented.

If one considers the data upon which the relationship of the hemolytic streptococcus to rheumatic disease has been postulated, the use of sulfonamides to prevent rheumatic recurrences seems to be rational enough. On the other hand, the study of other experienced workers suggests that there are many loopholes in the work thus far done in this direction. As for myself, I am not thoroughly convinced.

It may be that too little sulfonamide is being given to these patients. On the other hand, it is well established that the patient may develop resistant strains to the sulfonamides. It is quite possible that we may be forced to abandon this entire form of sulfonamide therapy because of the by-effects it may have on the blood of the patient and, in a few cases, upon renal function. I do not know the real status of protecting patients against rheumatic recurrences with sulfonamide therapy. I have not entirely abandoned it in my practice but I do not rely too much upon it.

Diagnosis. Judgment as to when rheumatic activity has terminated poses an important problem. We have to decide when we can again mobilize the patient. It is very gratifying to find that the experience with large numbers of children here leads to the same general thought as my experience with adults over a long number of years. The help of laboratory tests cannot be depended upon in making a diagnosis of rheumatic activity. I believe that in the final analysis, the clinical manifestations of the disease are far more important in diagnosis (as well as in arriving at the difficult decision as to when active rheumatic disease has ceased) than is reliance upon any single test or combination of laboratory tests.

It was satisfying for me to find that this attitude toward clinical judgment is the one held here. Dr. Taran tells me that many patients whose sedimentation test, temperature, pulse rate, vital capacity and hemoglobin content have become normal may remain in the active stage of rheumatic dis-

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ease. He tells me that children often tell the story of rheumatic activity in their behavior. These children, when left to their own devices, tend spontaneously to curtail their physical activities; when possible, they retire to more sedentary ways of behavior. Unfortunately, this is not as common in my experience with the adult. The adult will force himself to go ahead. He resents a period of economic inactivity and resents that behavior which classifies him as being an invalid. I think, therefore, that judgment as to the termination of rheumatic activity in the adult is even more difficult than in the child.

Rheumatic Activity. We know that rheumatic activity in the adult manifests itself in several different ways. Some patients have a single attack with no recurrences throughout the remainder of their lives. More commonly, we find the polycyclic type in the adult as well as in the child. I am inclined to believe that if the patient were cared for adequately during each one of these attacks, he might well end his active rheumatic career with relatively minor cardiac damage. While he may have definite valvular scarring, he may be expected to carry on with little or no cardiac disability into late adult life. In some of these polycyclic types, more significant damage is done to the heart muscle than to the valves. Some of these cases continue to have mild rheumatic activity for years. This state is often most difficult to diagnose.

It is difficult for me to imagine that the structural changes which take place in the valves, as we see them in the adult, should be the result of an allergic reaction on the part of the patient. On the other hand, we have no good bacteriologic or immunologic way of detecting this mild, smoldering infection. Dr. Homer Swift considers throat cultures to be of great value in prognosticating reactivation of the rheumatic process. On the other hand, other observers do not find this of such important diagnostic help. I am rather impressed with the fact that many rheumatic patients, either during the period of rheumatic activity or between rheumatic attacks, have negative throat cultures; and on the other hand, many rheumatic patients with positive hemolytic streptococcal cultures in their throats do not have or develop active rheumatic disease. A positive throat culture does not, therefore, necessarily signify rheumatic activity.

Classification of Rheumatic Heart Disease in in the Adult. I would be inclined to classify rheumatic heart disease, as seen clinically in the adult, into four very general categories: (1) Active rheumatic fever with evidence of carditis, endocarditis, pericarditis —one or more of these combined. (2) Patients who do not show evidence of active rheumatic disease but who have healed valvular lesions. I am excluding myocardial lesions from this group, as we have no ready means of diagnosing these clearly. This group, therefore, includes cases who show physical signs of valvular disease plus a history of one or more rheumatic manifestations in childhood. (3) A combination of type 1 and type 2. In this type 3, we have probably, the commonest form of rheumatic heart disease. This is the form of active rheumatic infection with residual valvular scarring. It is the most difficult type to treat. These patients do not respond to the usual methods of treatment. Their cardiac manifestations are not relieved as effectively as usual by the commonly used types of cardiac therapy. I think it is safe to say that the patient who does not respond to the usual forms of therapy has active rheumatic carditis. It seems as if rheumatic infection interferes with the cardiac response to our available therapeutic procedures. We find that we can go only so far in controlling the cardiac symptoms with bedrest, digitalis and diuretics. (4) The same as type 3 but with an additional infection, i.e., bacterial

endocarditis. This occurs most commonly in the form of subacute bacterial endocarditis and is generally due to the viridans type of streptococcus.

This classification into four types does not bring out the fact that active rheumatic carditis is possibly as common in the adult as it is in the child. Those of us who deal with adult rheumatic heart disease are often impressed with the frequency with which cardiac symptoms are associated with "activity."

It is generally accepted that the most characteristic manifestation of rheumatic activity is the Aschoff body. It is fair to say that if autopsies on the rheumatic adult were done with sufficient care and serial sections of the heart were studied, we would be surprised to find that the great majority of adults with rheumatic heart disease who were considered to be clinically inactive, really show histologic signs of rheumatic activity. This observation is of the utmost importance in relation to the discussion of therapy aimed at relieving cardiac symptoms in the rheumatic patient. In the adult as well as in the child, the only manifestation of rheumatic disease which can definitely give us help in prognosis is rheumatic activity. I would call your attention to the fact that age does not prevent rheumatic activity. That has been well proven by postmortem examinations.

Cardiac Manifestations. I think we must bear in mind that the clinical signs of valvular damage as manifested during active rheumatic disease do not necessarily foretell the degree of valvular damage that may be present a year later. The scarring process is a gradual and progressive one. Experience has shown that it often is not safe to form a judgment early in rheumatic disease as to subsequent myocardial damage. I prefer to wait from six months to a year before estimating such damage.

Mitral stenosis as a manifestation of rheumatic disease has no prognostic value, except in so far as it is probably better if this manifestation is postponed until early adult life than if it appears in childhood. I do not know why that is so. I think it would take a vast number of cases to determine the truth of this concept.

Auricular fibrillation of transient type appears frequently in the course of rheumatic disease. In my experience, this occurrence should be considered as one of the manifestations of rheumatic active carditis. One must bear in mind, however, that it may become a permanent arrythmia and therefore, be present in a patient who no longer has active disease. It has been suggested that the prognosis is somewhat better in the presence of auricular fibrillation than when it is absent. I do not know of any carefully conducted studies which substantiate this view. There is certainly no question that when auricular fibrillation supervenes in a case of congestive heart failure, control of the cardiac rate is more readily effected than when auricular fibrillation is absent.

There is one point in the literature with which my experience disagrees. It has been said that rheumatic pericarditis is one of the most serious prognostic manifestations of heart disease. The chance of developing the disease in other structures of the heart is greater in pericarditis—so they tell us—than in any other single manifestation of rheumatic disease. In my own experience, particularly in adult rheumatic disease, I am impressed with the fact that rheumatic pericarditis, if that has been the chief manifestation, gives a rather good prognosis. Naturally, in such patients the myocardium may suffer. But again, this has not been my experience. Most of the patients I have observed, return to the pre-pericarditic level after an attack of acute rheumatic pericarditis.

I would particularly call your attention to the confusing picture of healed valvular lesion in an active rheumatic heart with

early or beginning bacterial endocarditis. The differential diagnosis is often extremely difficult. We may have embolic phenomena in both. We certainly have fever in both. Secondary anemia is also found in both instances. In other words, the clinical picture may be essentially the same. There are few clues to differentiate rheumatic activity from early subacute bacterial endocarditis. One patient, as a matter of fact, presented just such a picture. He had some fever which was low-grade and not bothersome. It was an enlarged liver that called his attention to the illness. He lost his desire to work. Careful examination at least twice daily did not disclose any other phenomena, and one was inclined to diagnose this case as reactivation of old rheumatic disease. His white blood count and sedimentation rate were normal. His murmurs had not changed. If it were not for three successive positive Streptococcus viridans cultures, we should have treated this patient as having active rheumatic carditis. After obtaining the positive cultures, penicillin therapy was instituted and within forty-eight hours the entire picture changed. The temperature dropped to normal, the patient begain to gain weight and markedly improved within a short time.

I should like to call your attention to one more clinical manifestation of rheumatic disease not ordinarily emphasized in clinical diagnosis. I refer to recurring pulmonary infarction. I am speaking of the patient who runs a low-grade temperature and from time to time has signs in the chest but fails to respond to the usual therapy directed toward heart failure. This patient very likely has pulmonary manifestations which must be regarded as being part of the picture of active rheumatic disease.

Treatment. In the past few years, several experiments have been made on the use of massive doses of salicylates and on the administration of these drugs intravenously. On the latter point, I can see no advantage in giving salicylates intravenously rather than orally since they are rapidly and well absorbed by the gastrointestinal tract. In our present state of knowledge, we should consider salicylate therapy only as a symptomatic measure, particularly effective during the painful manifestations of rheumatic polyarthritis, but not a specific means for the treatment and cure of rheumatic disease.

Convalescence in the adult suffering from rheumatic heart disease is approximately the same as it is in the child. We should wait until we are convinced by all the evidence available to us at present that rheumatic activity has ceased. Then we should wait a little while longer, perhaps a few weeks, before permitting the patient to resume physical activities. The patient may then progress just as rapidly as his condition permits. In most instances, when his active disease is treated properly he will recover very rapidly during the quiescent period. Unfortunately, our general hospitals do not have adequate facilities to take care of patients of this type. It is obvious that we need many institutions which are set up primarily for the care of the rheumatic patient who is not acutely ill and yet not quiescent, institutions whose aim it is to treat the patient until all evidence of rheumatic activity is terminated.

As to the time when the patient can be mobilized, it seems to me that it requires considerable clinical judgment to make this decision. Whatever the clinical signs may mean, my experience tells me that they are the most accurate of our tests for determining when the patient's rheumatic activity has ceased and when he can be mobilized. We hope that more objective criteria will be developed in the near future.

DISCUSSION

QUESTION: In the treatment of inactive rheumatic disease do you think that restric-

tion of activities would prevent rheumatic recurrences?

DR. EGGLESTON: I have never seen any evidence that it does. I think we in the medical profession like to err on the side of conservatism. But I do not think that physical activities, if kept within the limits of the patient's heart capacity, have any particular influence on the recurrence of rheumatic activity. What is your opinion in this matter, Dr. Taran?

DR. TARAN: Our experience with children and with young adults is precisely the same as yours. What the physician wants to know, I believe, is how to manage an adult rheumatic cardiac patient in order to prevent further cardiac damage and, above all, rheumatic recrudescences. Should the adult rheumatic cardiac patient be dismissed from the list of follow-up patients until such time as rheumatic activity occurs, or should he be kept under careful medical supervision during the rest of his life? In children and young adults, we are inclined to take a middle course. While we believe that these patients should be encouraged to resume normal activities as long as their rheumatic disease is quiescent, we do not like to lose sight of them for fear of overlooking an attack of mild rheumatic activity. What is your experience with the adult in this regard, Dr. Eggleston?

DR. EGGLESTON: I am also inclined to straddle the question. I allow patients to do anything within their myocardial capacity. I urge them into as hygienic a mode of life as possible. I encourage them to live as much as possible in the open air and sunshine, and in general, maintain as high a state of general physical health as possible. The advice is much like that given to a patient with arrested tuberculosis. In addition, I advise them to shun those in their environment who have frequent infections. But, I do not limit their life's activities unless it is evident that their cardiac reserve is low.

QUESTION: Do you believe that if a patient has quiescent rheumatic heart disease, full vigorous physical activity is likely to precipitate congestive heart failure at an earlier age, due to strain of the heart muscle?

DR. EGGLESTON: I think that in the absence of rheumatic activity, there is no evidence that physical work will precipitate cardiac failure. In other words, if the patient can perform any vigorous act without cardiac symptoms, he will sustain no harm from that act. I allow such patients to play games, indulge in sports, and even play vigorous tennis. I have seen no harm from it.

QUESTION: Is there any explanation why some patients will have only one attack and others have repeated attacks of rheumatic active disease?

DR. EGGLESTON: I have no idea. It is a fact that certain patients suffer one attack and go through life without any recurrences. I do not know why. In fact, I think it is safe to say that we do not know very much about the immunology of rheumatic fever. I do not even know that rheumatic fever is a bacterial infection although all evidence points in that direction more than in any other direction. Why one patient should get recurrences and another should not, is still a mystery.

QUESTION: Would you say then, that our habit of excluding children and young adults from competitive sports during the quiescent period of rheumatic disease is not based upon solid evidence?

DR. EGGLESTON: If the patient is symptom-free, I do not restrict him in any way. I think it is reasonable to say that once a patient has healed rheumatic disease, he can be classified in the same way as a patient who has had an incision into his body, an incision which has healed. I am inclined to say that such scars as may be left in the heart muscle which had not given any subjective or objective symptoms can be disre-

garded from the point of view of demands placed upon the heart muscle.

DR. TARAN: I think it is only fair to state, however, that the habit of keeping rheumatic children out of competitive sports is based upon the premise that since these children are not watched very carefully and frequently, one might overlook mild, smoldering, active rheumatic disease. It is during the period of active disease that we wish to protect the child from vigorous exercise. I am quite certain that if we could watch these children carefully, and be sure that there was no evidence of rheumatic activity, we would permit them any form of physical activity within the limits of their cardiac ability, irrespective of the presence of definite evidence of advanced valvular disease.

QUESTION: Is there any evidence that makes us believe that keeping patients in bed for a long period of time predisposes to pulmonary emboli?

DR. EGGLESTON: Yes, our habit used to be to keep such patients in bed for a long time. I do not now. I do not believe in rigid inactivity, even in a case of mild active rheumatic disease. Even in this instance, we do not get into difficulty if we do not impose excessive restrictions on these patients. Movement of the arms and legs is rather important.

QUESTION: Is there any special hazard in pregnancy and labor in rheumatic heart disease?

DR. EGGLESTON: I can dodge that question by saying I am not an obstetrician. We follow all our pregnancy cases very closely, together with the obstetrician. It is my experience that if during the course of pregnancy there is no evidence of a failing heart, it is safe to permit the patient to carry through and deliver normally. It is only when the heart shows definite evidence of failure that we interrupt the pregnancy. We do believe, however, that labor should be eased as much as possible. In my experience, it is perfectly safe to permit the patient to go through the entire pregnancy while being controlled with digitalis. There is, of course, the other side of this problem—that is, a rheumatic cardiac patient who becomes pregnant is likely to lose the baby.

QUESTION: Would you favor digitalizing a patient with heart disease who becomes pregnant but who does not show signs of failure?

DR. EGGLESTON: I do not see any indication for that. We can nowadays digitalize a patient so rapidly, and with such a high degree of certainty and safety, that I do not see any reason for pre-digitalizing before evidence of heart failure appears. I think, however, that it is important to keep these patients under close enough observation to be able to pick up early or incipient decompensation.

QUESTION: Would you consider a slight increase in dyspnea in a pregnant patient with rheumatic heart disease as a sign of heart failure?

DR. EGGLESTON: First, we have to weigh all the clinical findings before stigmatizing a patient as having cardiac insufficiency. However, a degree of dyspnea greater than what would be normal for a patient who is pregnant should be considered as sufficient evidence of oncoming cardiac insufficiency. The apparent dyspnea that one sees in women after the fourth month of pregnancy, however, may not be cardiac.

QUESTION: Some years ago, at a meeting of the Heart Association, a paper was presented on the subject of pregnancy and rheumatic heart disease. The thesis at that time was that mitral stenosis gave a poorer prognosis in pregnancy and labor than minimal signs of heart failure. Do you subscribe to that, Dr. Eggleston?

DR. EGGLESTON: Frankly, I have not had sufficiently wide experience with that group of women to be able to form a sound judgment on that subject. It is my impression,

however, that from the point of view of pregnancy and labor the extent of valvular damage is less significant than insufficiency of the heart muscle.

QUESTION: Is active rheumatic disease an indication for terminating pregnancy in a case in which the heart is well compensated?

DR. EGGLESTON: I think active rheumatic carditis is a valid reason for terminating pregnancy from the point of view of both the mother and the fetus.

QUESTION: Is there any risk in interfering with the pregnancy in such a case?

DR. EGGLESTON: Very small.

QUESTION: Is the risk smaller than carrying the baby through for nine months?

DR. EGGLESTON: I think so. It is my impression that rheumatic patients who have fairly good hearts are good operative risks. I would go further and say that patients with heart disease are good operative risks except when there is definite evidence of heart failure or a high degree of active carditis.

QUESTION: Since we are on the obstetrical angle, I have come across a statement recently that when a rheumatic patient is found to have a rise in pulse rate above 110, and a respiration rate above 24 during the first stage of labor, digitalization is indicated. What is your experience in this direction?

DR. EGGLESTON: It is very reasonable to state that in a rheumatic cardiac patient, or in any cardiac patient, a rise in respiration rate during the first stage of labor should be considered a sign of early decompensation. Digitalization therefore is indicated.

DR. TARAN: This discussion of rheumatic disease in the adult may be summarized as follows: It was pointed out that while the various manifestations of rheumatic disease may differ somewhat in the adult and in the child, the dominant consideration is the active rheumatic process and not the end result of cardiac damage. The important question in the management of rheumatic disease in the adult is when the activity has ceased and quiescence has begun. Treatment of rheumatic disease in the adult does not differ from that in the child since the important policy in treatment is good medical care during the acute process in both adult and child. A good deal of stress was placed upon clinical assessment of symptoms and signs as against reliance upon the laboratory methods commonly used for the diagnosis of acute rheumatic fever.

A workable classification for the types of rheumatic disease encountered in the adult was presented and some of the more unusual manifestations of rheumatic heart disease were described.

Some of the modern concepts of treatment were discussed but it was pointed out that continued bedrest during the active process still remains the most important means of discouraging further cardiac damage. Return to completely normal active life is advised in patients with rheumatic disease in whom it is reasonably certain that the active disease has terminated.

Treatment of Acute Rheumatic Fever and Acute Rheumatic Heart Disease*

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IT would seem presumptuous to attempt to discuss the treatment of rheumatic disease in one session. Such disproportion in the assignment of time might lead one to assume that this aspect of the subject is relatively unimportant. While it must be admitted at the outset that no specific remedies have been forthcoming, I believe we have learned a great deal about the treatment and management of acute rheumatic fever in the last few years. Experience with this "non-specific" treatment has already accumulated evidence to show that the outlook for the patient with rheumatic disease has definitely improved.

There are two schools of thought with regard to treatment of this disease. There are those who are definitely discouraged and have the attitude that rheumatic disease is a hopeless chronic illness for which little or nothing can be done. These workers in the field believe that all our energy and interest should be devoted to the study of the cause rather than the treatment of rheumatic disease. The second group of workers in this field believe that rheumatic disease should be treated somewhat like tuberculosis. We had gone a long way in the management of tuberculosis before the tubercle bacillus was discovered. Similarly, a good deal of progress in the treatment and management of rheumatic disease may be expected before the etiology is known.

PREVENTION OF RHEUMATIC RECURRENCES

Chemotherapy. The factors which stimulated the vigorous attempts to prevent rheumatic disease are rather obvious. We know that rheumatic disease has a tendency to recur; and the more attacks, the more extensive the cardiac damage. The frequent combination of hemolytic streptococcal infections with rheumatic disease, and the ease with which streptococcal infections can now be prevented by chemotherapy all led, in recent years, to a flurry of attempts to prevent rheumatic recurrences. I believe it is fair to say that final judgment with regard to the efficacy of sulfanamides in preventing rheumatic recurrences must be deferred until further rigidly controlled studies are made.

Climate. Some years back, a great deal was said with regard to the effect of subtropical climate upon the natural history of rheumatic disease. Many patients have been sent to Florida, Arizona and Southern California in the hope of preventing rheumatic recurrences. The results to date do not give us enough solid evidence to show that residence in a subtropical climate definitely modifies the course of rheumatic disease. It must be said, however, that the appealing character of this form of therapy may definitely have its psychologic rewards, and may confuse final evaluation

From the St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, N. Y.
* One of the Seminars on Rheumatic Fever conducted at St. Francis Sanatorium for Cardiac Children, Roslyn, Long Island, New York, October 30, 1945.

of the effect of climate, as such, upon the disease.

Salicylates. Many clinics, both in England and this country, have used salicylates in varying dosage as a prophylactic agent against rheumatic recurrences. Some clinics in England have administered salicylates to ambulatory patients over a large number of years. We have tried a similar experiment, using small doses of sodium salicylate during the winter months in patients who might be susceptible to rheumatic recurrences. To date, we have no evidence to prove that this form of therapy prevents rheumatic recurrences.

Vaccination. Many attempts have been made to vaccinate or inoculate patients with hemolytic streptococcal vaccines in order to prevent rheumatic recurrences. More work needs to be done in this direction to prove the relationship of such therapy to the prevention of rheumatic recurrences. It would seem to me that clearer insight into the immunologic responses of patients with rheumatic disease must be obtained before proper evaluation of this method of prophylaxis can be made.

Vitamins. The significance of vitamin B and, in recent years, vitamin C has not been fully explored in the matter of preventing rheumatic disease. The first encouraging evidence with regard to the rôle that vitamin C plays in rheumatic disease has been somewhat dimmed by lack of confirmation of reported results.

In summary, therefore, one is compelled to state that no method thus far proposed in the prevention of rheumatic recurrences can be relied upon to modify the natural course of rheumatic disease.

TREATMENT—ACUTE PHASE

Salicylates. Of all the therapeutic agents that have been used in the treatment of rheumatic disease, salicylates have stood the test of time. Many years ago, large doses of salicylates were used with often startling therapeutic results. However, since untoward effects were observed frequently, and since it cannot be shown that salicylate therapy is a specific form of therapy, the use of massive doses was gradually discouraged.

The recent statement of Coburn that massive salicylate therapy may prevent the stigmata of heart disease reawakened interest in this form of therapy. However, evaluation of any therapeutic agent for rheumatic disease is fraught with so many difficulties and pitfalls that it is not easy to determine whether salicylates are beneficial or not. Suppression of the sedimentation rate does not always signify cessation of the active rheumatic process. Subsidence of all clinical and laboratory evidence of active rheumatic disease does not always mean that significant heart damage may not appear years later, without obvious recurrences of rheumatic disease. On the other hand, it has been observed that massive doses of salicylates often produce startling therapeutic results in making the patient symptom-free.

Our experience with salicylate in large or massive dosage may be summarized as follows: (1) Rheumatic polyarthritis responds promptly and effectively to large doses of salicylates. This result can be obtained by oral as well as intravenous use of salicylates. The intravenous route does not offer any advantage over the oral route. Massive doses of salicylates in this group of cases did not present any important toxic manifestations of salicylism. (2) Massive doses of salicylates used early in rheumatic carditis in children seem to produce equally prompt and effective results. Intravenous therapy in this group may be hazardous. (3) Small doses of salicylates do not seem to affect the course of rheumatic carditis. In this group, one finds that when salicylates are withheld or given in small doses evidence of active rheumatic disease continues for

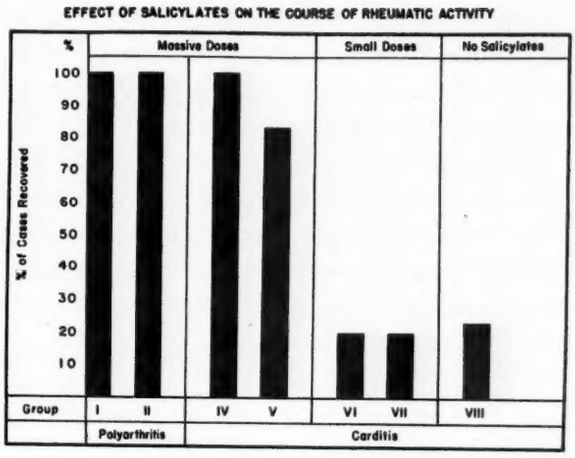
weeks and months following cessation of therapy. (Fig. 1.) (4) Finally, massive doses of salicylates present definite hazards.

Sanatorial Care. The short period of observation and the small number of cases so far observed under sanatorium care preclude the formulation of statistically significant conclusions as to the lasting effects of sanatorium care. However, close observation of small groups of cases at the sanatorium, and of comparable groups of rheumatic children who did not receive sanatorium care, justifies certain deductions.

A large proportion of the children treated here at St. Francis are admitted from the cardiac clinic and the wards of the Kings County Hospital. The total number of Kings County children treated at the sanatorium during the first seven-year period was 373. During the same period of observation, 312 children were chosen from the clinic and wards of the same hospital as controls. Since inadvertent bias may play a significant rôle in the choice of cases for sanatorium care, painstaking efforts were made in choosing the control group, case for case. No convalescent care of any sort was offered to the control group of children.

The two groups of children were comparable as to age, age at onset of rheumatic history, number of rheumatic attacks, the extent of cardiac enlargement, and the incidence and type of rheumatic active infection observed at the beginning of the study period. (Table I.) In addition, the two groups compared well as to the type of home environment before the study began and at the end of the period of observation. The results were as follows:

1. *Rheumatic Recurrences:* The number of rheumatic recurrences following sanatorium care is significantly smaller than in the control group. Both groups of children show a marked decline in recurrence rate as the time from onset of the rheumatic disease increases. The treated group, however,



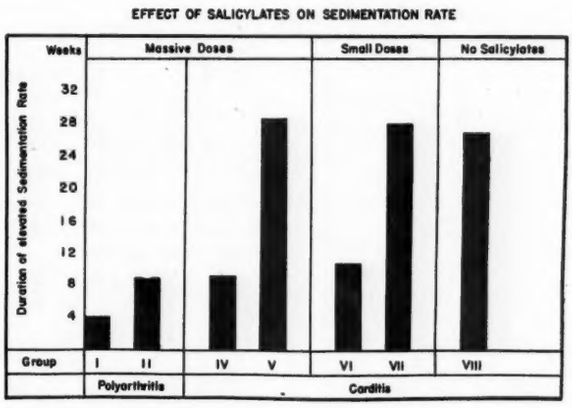


FIG. 1

FIG. 1. Group I: Children who received intravenous salicylates for rheumatic polyarthritis. Group II: Children who received massive oral doses of salicylates for rheumatic polyarthritis. Group IV: Children with rheumatic carditis who received massive doses of sodium salicylate by mouth at the onset of the rheumatic episode. Group V: Children with rheumatic carditis who received massive doses of sodium salicylate by mouth; treatment begun several weeks after onset of carditis. Group VI: Children with rheumatic carditis who received the usual small doses of sodium salicylate at the onset of rheumatic carditis. Group VII: Children with rheumatic carditis who received the usual small doses of sodium salicylate; treatment begun weeks after the onset of the rheumatic episode. Group VIII: Children with rheumatic carditis who did not receive any salicylates during the entire period of rheumatic activity. (From *J. Pediat.*, 27: 59–68, 1945. Courtesy of the C. V. Mosby Company, St. Louis.)

seems to escape a significant number of recurrences. The decrease in recurrence rate in this group is most marked at the beginning of the post-sanatorium period. (Fig. 2.)

2. *Cardiac Enlargement:* In our experience, the extent of cardiac hypertrophy in children seems to be a more accurate index of cardiac damage than the extent of valvular involvement. Children with large hearts have a much poorer prognosis than those whose hearts are only slightly enlarged. In this study, we considered a heart as enlarged only if the enlargement was unequivocal and diagnosed as such, both on clinical examination and by roentgen studies.

Table I

Comparison of treated and control groups of children at the first observation

	Control group	Treated group
Number of children studied	312	373
At the beginning of period of observation		
Average age (yrs.)	9.35	9.22
Average age at onset (yrs.)	7.38	7.37
Duration of rheumatic history (yrs.)	1.97	2.10
Number of attacks per child	1.67	1.82
Percent of children with unequivocal cardiac enlargement.	12.5	12.5
Percent of children having active rheumatic disease at the beginning of study.	18.7	19.8

At the beginning of the period of observation about 12.5 per cent of both the treated and the control groups of children showed cardiac enlargement. The average age of our children at the beginning of the study was nine and a half years and the majority of them were seen about two years after the onset of rheumatic history. As these children grew older, the percentage incidence of cardiac enlargement increased in both groups; but the increase in the number of patients with large hearts was significantly greater in the control group than in the treated group. (Fig. 3.)

3. *Mortality:* It was pointed out by Coombs that before the question of life expectancy in rheumatic patients can be answered, at least thirty years must be allowed to elapse between the beginning and the end of observation in a large number of patients. Our numbers are small and the lapse of time even smaller. Nevertheless, the marked difference between the number of deaths in the sanatorium group as compared with the control group of cases is worthy of comment. Of the total of 373 children treated at the sanatorium, eight died of rheumatic disease. Of the control group of 312 children, twenty-one were dead of rheumatic disease at the end of the same period of observation.

The mortality and life expectancy studies of Dr. May Wilson show that at the end of the first year from the onset of the disease, 2 per cent of the children died of rheumatic disease; by the fourth year, 5 per cent; by the seventh year, 10 per cent; and by the end of the eighth year, over 16 per cent. Our findings for the control group of children are analogous to those of Dr. Wilson. The treated group, however, shows a significantly lower mortality rate. (Fig. 4.)

In summary, it may be stated that seven years' experience with the sanatorium method of care for rheumatic children seems to show that this type of care favorably in-

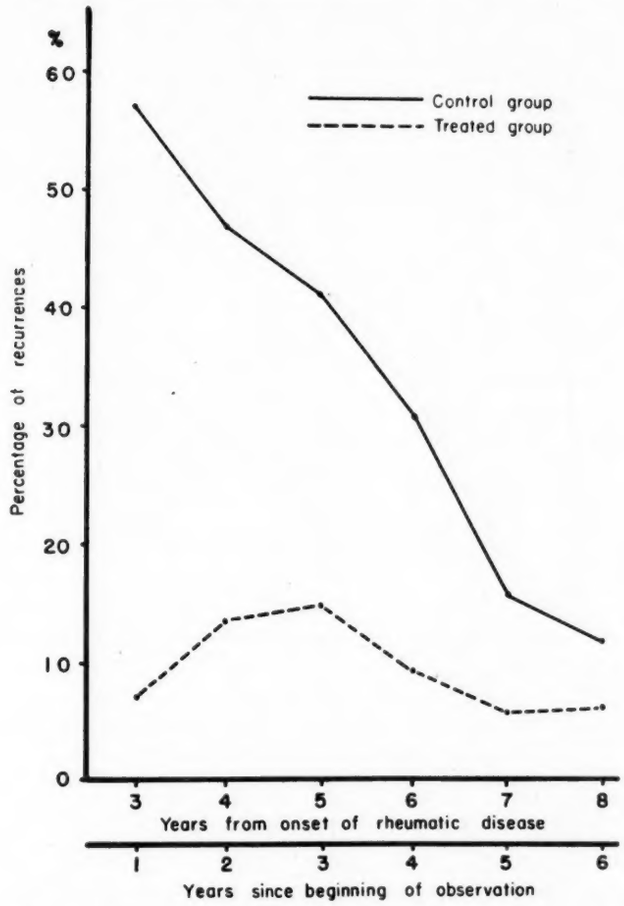


FIG. 2. Percentage incidence of rheumatic recurrences in relation to lapse of time since onset of rheumatic disease.

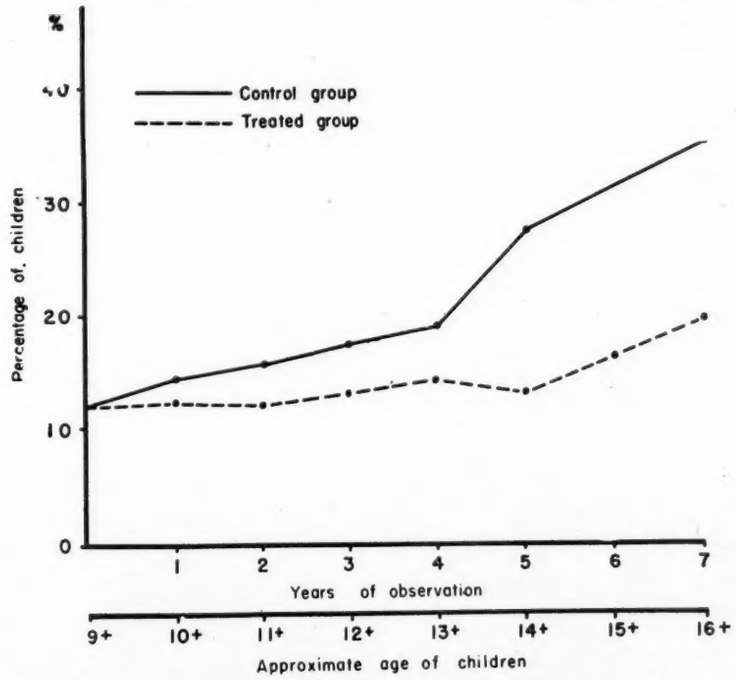


FIG. 3. Percentage incidence of children showing unequivocal cardiac enlargement.

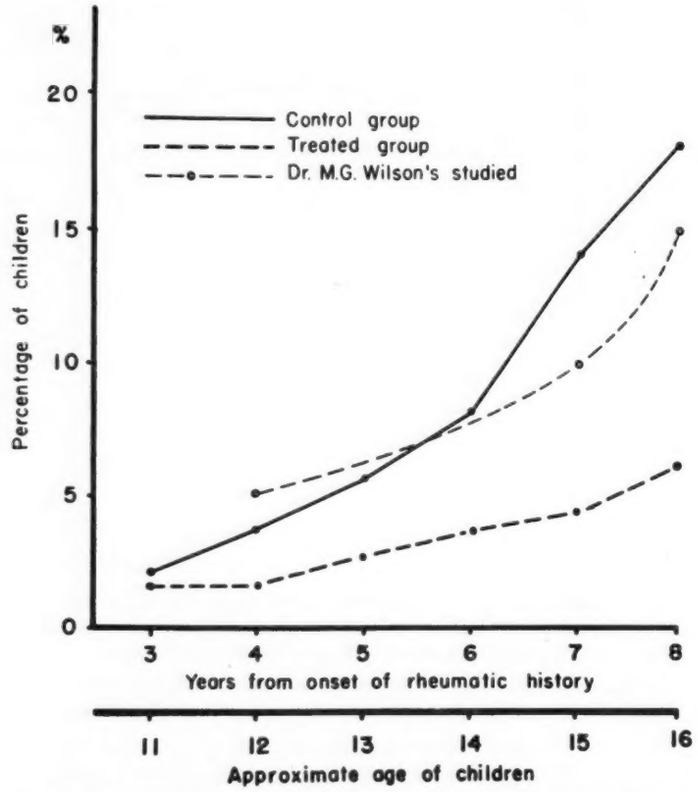


FIG. 4. Percentage incidence of deaths in rheumatic children in relation to lapse of time since onset of rheumatic disease.

fluences the course of rheumatic disease in children. It seems reasonable to assume that the significant decrease in the recurrence rate at the early stage of rheumatic disease when treated at the sanatorium may, in part, explain the low incidence of cardiac enlargement and the significantly lower mortality rate observed in the treated group of children.

TREATMENT OF RHEUMATIC HEART DISEASE WITH FAILURE

It is generally agreed that heart failure in rheumatic disease is almost always accompanied by rheumatic carditis. Thus, it is the belief of most clinicians that the pattern of failure in this form of heart disease differs in some respects from that observed in other forms of heart disease, in which the mechanical type of failure predominates. It is a reasonable assumption, therefore, that the usual form of therapy used in rheumatic heart failure does not produce the beneficial effects usually observed in arteriosclerotic, hypertensive and other forms of heart failure. The use of digitalis, for instance, in rheumatic heart disease with failure rarely, in our experience, produces the desired effect. Mercurials and other diuretics do not produce the same startling diuresis in acute rheumatic carditis with failure as they do in other forms of heart failure.

Digitalis. Some observers believe that digitalis should not be used in acute rheumatic carditis with failure. Sir Thomas Lewis believed that "the use of digitalis for failure with congestion in rheumatic infection is not recommended." Derick, in 1936, stated that "the benefit of digitalis in active rheumatic carditis with decompensation is questionable." Tung, in 1936, made the observation that "although in general, auricular fibrillation with a rapid ventricular rate, is an indication for digitalis, the onset of this

rhythm in patients who have received large doses of digitalis, constitutes an indication that a toxic effect of digitalis is present. Further use of the drug might give rise to ventricular tachycardia or fibrillation or even irreversible cardiac damage." Schwartz and Levy during 1930 and 1931, found that "digitalis does not produce beneficial effects in rheumatic cases with decompensation even in afebrile cases."

Our studies on the use of digitalis in acute rheumatic carditis with failure agree, in the main, with these observations. We are impressed, however, with the fact that certain types or certain patterns of failure react somewhat more favorably to digitalis than others and that certain forms of acute carditis are much more sensitive to the toxic effects of digitalis than others. (Fig. 5.)

We have rarely observed any beneficial effects from digitalis therapy in acute rheumatic pancarditis with heart failure. Toxic effects of digitalis occur early, very frequently before the complete digitalization dose has been given. Several instances in which complete digitalization with the single dose method was attempted resulted in paroxysmal ventricular tachycardia and, in one instance, in ventricular fibrillation. Our experience would seem to warn strongly against the use of digitalis in this form of heart failure.

We have been unable in the vast majority of instances to relieve cardiac failure with digitalis when the presenting symptoms were those of left-sided failure. In such cases, depression of the ST interval and inversion of the T wave on the cardiogram, as well as premature ventricular contractions, occur early in the period during which digitalization is carried out. It would seem, therefore, that in this type of rheumatic heart failure digitalis is of little or no help.

In a few instances, when the presenting symptoms are both left- and right-sided failure, digitalis seems to relieve some of

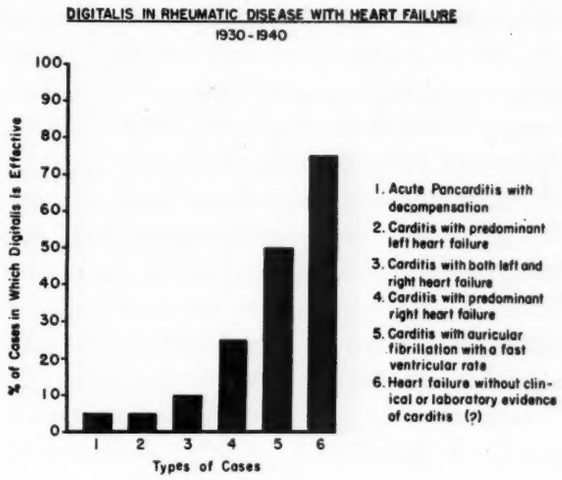


FIG. 5.

these symptoms. In this group of cases, therefore, it is worth trying.

In the rare instance in which the patient shows almost true right heart failure, digitalis seems frequently to produce the desired effect. Our observation, therefore, suggests that in this group digitalis should always be tried.

In our experience, only half of the cases with acute carditis with auricular fibrillation can be controlled with digitalis. In one of every two cases of auricular fibrillation suppression of the rapid ventricular rate could not be accomplished with complete digitalis therapy, and toxic effects of digitalis occurred before visible effective results could be obtained.

It is questionable whether one ever sees rheumatic heart failure without active rheumatic disease. Occasionally, one is impressed with the fact that all laboratory and clinical evidences of carditis are absent and the patient presents unequivocal signs of advancing failure. While it is admitted by pathologists that histological examination of these hearts would undoubtedly show evidence of rheumatic activity, the active process must be at a level which is below the clinical horizon. These cases react in the classical way to the use of digitalis.

Mercurial Diuretics. From time to time one sees in the literature a report on the use

of some of the xanthine group of diuretics in rheumatic heart disease. Our experience shows that there is no benefit to be gained from withholding mercurial diuretics; that these are the most effective diuretics; and that toxic effects from mercurials are extremely rare. We are impressed with the fact that the use of mercurials in rheumatic heart failure occupies a more important place than in failure from other causes. Not infrequently this form of therapy is a life saving measure. Advancing cardiac edema can be controlled effectively by means of mercurials until the active carditis is past and cardiac efficiency is increased.

Oxygen Therapy. The use of oxygen as a therapeutic agent in heart disease has been explored both in England and in this country for the past twenty-five years. Barach and his associates have studied the effect of oxygen therapy in various types of heart disease and concluded that in congestive heart failure and in acute coronary thrombosis oxygen is very often a life-saving measure. Poulton in England has demonstrated that patients suffering from rheumatic carditis with or without failure showed marked improvement when treated in a 50 per cent oxygen atmosphere. Our experience with oxygen therapy in rheumatic carditis in children in the main confirms the observations of Poulton. In cases with acute carditis of recent onset there is an immediate drop in temperature and pulse rate. The clinical behavior of the patient, the unequivocal improvement in cardiac reserve, and the dramatic removal of all subjective and objective signs of cardiac insufficiency, reflect the profound salutary effect of oxygen therapy upon cardiac physiology disturbed by acute rheumatic carditis. We are impressed with the fact that while rheumatic activity is not measurably shortened by oxygen therapy, the cardiac disability resulting from carditis is greatly minimized by decreasing the work of the heart during the acute inflammatory phase. In addition, our experience shows that residence in a high oxygen atmosphere during the course of acute carditis removes the disabling and most annoying symptom of cardiac fatigue so commonly observed in children suffering from acute rheumatic carditis. This symptomatic relief enhances relaxation, sleep and nutrition, factors which undoubtedly contribute to rapid and satisfactory recovery.

CONCLUSIONS

It is clear from this brief discussion that much remains to be learned about the treatment of acute rheumatic fever and rheumatic heart disease. The prevention of rheumatic recurrences with chemotherapeutic agents is still in the experimental stage. The use of massive salicylate therapy in acute rheumatic disease remains an important form of therapy in acute rheumatic polyarthritis and at the onset of acute carditis. Digitalis, in our experience, is of limited therapeutic use in acute carditis with failure; mercurial diuretics, used judiciously during this phase of the disease, seem to be a satisfactory substitute for digitalis therapy. Long residence in a 45 to 50 per cent oxygen atmosphere during the course of acute carditis offers a definite means for reducing the work of the heart during the acute inflammatory phase and, in our experience, minimizes the cardiac damage resulting from acute carditis.

DISCUSSION

DR. TARAN: The subject of treatment of acute rheumatic fever and acute rheumatic heart disease with failure is now open for discussion. Are there any questions?

QUESTION: Your statement on prevention of rheumatic recurrences seems to indicate that none of the proposed methods of prevention has proven to be efficacious. And yet, it has been the experience of many practicing physicians in recent years that the judicious

prophylactic use of chemotherapy seems to stop the progress of rheumatic recrudescences. Some of us have been impressed with the distinct improvement in the rheumatic status of the patient when he is transferred to a warm, dry climate. Occasionally one sees unmistakable progress in the natural history of rheumatic disease by careful attention to nutrition and vitamin intake of the rheumatic patient. Furthermore, we are told that rheumatic children in a good physical environment weather the storm of rheumatic disease better than those in a poor home environment. These more fortunate children have less recurrences and, by and large, sustain less cardiac damage. There should be some explanation for this testimony culled from everyday practice.

DR. TARAN: You are quite right that much testimony can be gathered in private practice to show that rheumatic disease can be treated effectively. I am, however, not certain that any such evidence exists to show definitely that rheumatic recurrences can be prevented by the methods you mention. A wide experience with these patients over long periods of time seems to indicate that good medical and nursing treatment of the acute phase of the disease is, for the present, the best insurance against so-called recurrences. We are impressed with the fact that in most instances recurrent attacks are reactivations of a subacute active process rather than truly *recurrent* attacks. Once the active process has come to an end, a recurrence is unlikely. This may explain the often striking difference in the end results in patients who receive careful medical attention and those who are neglected during the course of mild rheumatic activity. The incidence of rheumatic recrudescence after good sanatorium care is indeed small and matches favorably the good results obtained by a change of climate, chemotherapy and a high vitamin intake. In sanatorium care the principal aim is prolonged treatment of the acute phase until all clinical evidence of active disease has subsided. Change of climate or the institution of a special regimen of chemotherapy or nutrition may often be associated with a careful regard for other factors—more rest, less exposure to chilling, etc., all of which may have a salutary effect upon the mild, smoldering rheumatic process.

Much remains to be learned about rheumatic recurrence as distinct from reactivation. For the present, we are impressed with the fact that the therapeutic measures which seem to affect favorably the course of the active process of the disease insure, at the same time, the most effective way of preventing recurrences. Rheumatic activity, even of the mildest type, with manifestations that are subclinical, often needs only an apparently insignificant provocative stimulus to be transformed into a severe, stormy reactivation or "recurrence." Complete quiescence in children, in our experience, only rarely is followed by recurrent attacks.

QUESTION: We are told that sodium bicarbonate when given in conjunction with sodium salicylate depresses the salicylate level in the blood. Does bicarbonate, therefore, interfere with the therapeutic effectiveness of salicylates?

DR. TARAN: We have not found it difficult to reach an optimum salicylate level (350–400 micrograms) in the blood serum when bicarbonate was used. Our custom is, however, to use small doses of bicarbonate, not more than half the salicylate dose. Our success with salicylate therapy was obtained only when an optimum serum level was reached.

QUESTION: How do you recognize salicylate intoxication? What is the mechanism of the intoxication?

DR. TARAN: The clinical picture of salicylate poisoning has been known for many years. It is characterized by extreme dyspnea; irritability and restlessness; nausea and

vomiting; dehydration and eventually disorientation, paralysis, coma and death.

The mechanism of this intoxication is not known. Several theories have been advanced: (1) Acidosis leading to hyperpnea has been considered as the main underlying cause; there is little evidence for this thesis. (2) Direct stimulation of hypothalamic nuclei causes hyperpnea which leads to acidosis; the acidosis due to hyperventilation may cause an increased metabolic rate, and this in turn, depletes the glycogen reserve; some have shown a direct loss of glycogen in the liver, thus interfering with the hepatic enzymes. (3) Increased metabolic rate; not substantiated. (4) Prolongation of the prothrombin time is an important factor. Toxic injury to the small blood vessels is the primary lesion—increased permeability of vessels.

The pathological findings are: (1) generalized petechial hemorrhages, varying in size from pin-point to large hematomas, have been observed in the brain, lungs, myocardium and mucosa of the stomach; (2) general congestion of the organs.

We have not observed severe bleeding resulting from massive salicylate therapy. In our experience, the hypoprothrombinemia which occurs in massive salicylate therapy can definitely be prevented or reversed by the use of vitamin K in small doses.

Intoxication from sodium salicylate is rare, and should, for the present, be regarded in the category of idiosyncrasies. Since, however, it is used so extensively in rheumatic disease, these idiosyncrasies should be watched for with concern. While the hazard is real, we have observed definite and severe salicylate intoxication in only three cases in a period of ten years. This low incidence of severe intoxication may be due to early recognition of poor risks for salicylate therapy. About 3 per cent of the patients treated with massive doses are poor risks for this form of therapy.

QUESTION: What distinguishes sanatorium type of care from good home or hospital care? It is not possible to carry out a sanatorium type of care in the home of the patient or on the wards of a well equipped pediatric service?

DR. TARAN: Yes. There is certainly no magic in the word sanatorium. The sanatorium is established on the principle that rheumatic disease in children in the acute stage cannot be adequately treated under conditions present in the usual children's hospital. It is a disease of months' or years' duration and the active period, no doubt, lasts much longer than the clinical manifestations, as we understand them now, would seem to show. Careful and detailed observation of elusive manifestations of the subclinical phase of the disease are of importance in the matter of preventing reactivation and progressive cardiac damage. This patient attention given over a period of many months cannot be carried out in the impatient environment of a hospital for acute diseases.

Furthermore, the sanatorium is set up to deal with the many psychologic, educational and sociologic problems inherent in protracted illness. To carry out such a program, the personnel of the sanatorium must be trained for this specific task. Such trained personnel is not to be had, at present, in most hospitals established for the treatment of acute disease.

With good intentions and a full understanding of this disease by the physician, nurse and parents, sanatorium care can indeed be carried out satisfactorily in the home of the patient. But since rheumatic disease is a poor man's disease, private care at home is completely prohibitive financially for most of the patients.

QUESTION: It would seem from your statement that digitalis therapy in rheumatic heart disease with failure in children is of limited value. Is this true also in adults?

DR. TARAN: Some observers believe that cardiac decompensation in a rheumatic heart is always indicative of active rheumatic disease, irrespective of the age of the patient. In our experience with young adults, this seems to be true. In these, digitalis therapy is of limited value. It is well known, however, that so-called "pure" mechanical failure is much more frequently encountered in the adult rheumatic cardiac than in the child. In these, digitalis produces the usual favorable effects. Auricular fibrillation is more common in the adult than in the child. In this group digitalization is the therapy of choice. On the other hand, one is frequently impressed with the number of digitalis failures in adult rheumatic cardiacs particularly when the symptoms of decompensation are predominantly those of left-heart failure. When the signs of active carditis are clear, digitalis therapy is often disappointing in the adult as well as the child.

QUESTION: Is there any physiologic explanation for the apparent beneficial effects of oxygen in acute carditis?

DR. TARAN: Much remains to be learned about the mechanism of oxygen therapy in heart disease in general and in rheumatic carditis in particular. A full answer to your question cannot, therefore, be given.

I am impressed with the concept, however, that overactivity of the acutely inflamed heart muscle fiber must be physiologically unsound and may be responsible for disturbance of the chemical and mechanical integrity of the heart muscle. An accelerated cardiac rate may further deplete cardiac efficiency by diminishing diastolic coronary filling, accentuating an already existing anoxemia of the heart muscle. Anoxemia of the heart muscle results in further disturbance in cell metabolism of the muscle fiber.

It is reasonable to assume that a form of therapy which diminishes cardiac overactivity during the course of the acute inflammatory process might prevent the damaging end result of acute carditis. A significant decrease in cardiac rate alone diminishes the work of the heart, the working capacity of which is already impaired by local tissue anoxia. Decrease in cardiac rate might further improve the local tissue oxygen want by improving coronary filling. If this form of therapy would in addition raise the oxygen saturation of the arterial blood, which is critically diminished in cardiac patients, cardiac disability could be significantly prevented.

In our experience oxygen therapy in rheumatic carditis meets all these requirements.

SUMMARY

The treatment of acute rheumatic fever and acute rheumatic heart disease with failure was discussed in this morning's seminar. The efficacy of chemotherapy in the prevention of rheumatic recurrences was questioned. Massive salicylate therapy for acute rheumatic fever was considered effective in changing the course of rheumatic polyarthritis and early carditis. The benefits derived from sanatorium type of care for the protracted case of rheumatic disease were described and the principles underlying the aims of this type of care were delineated. Digitalis in the treatment of acute rheumatic carditis with failure was considered of limited value. Finally, the use of high concentrations of oxygen in the treatment of acute carditis was discussed. It was pointed out that while oxygen therapy may not influence the duration of rheumatic activity, it seems to lessen the cardiac disability resulting from carditis. Some of the physiologic principles responsible for the salutory effects of oxygen therapy were presented.

Conference on Therapy

The Dose of a Drug

THESE are stenographic reports of conferences by the members of the Department of Pharmacology and of Medicine of Cornell University Medical College and New York Hospital, with collaboration of other departments and institutions. The questions and discussions involve participation by members of the staff of the college and hospital, students and visitors. A selected group of these conferences is published in an annual volume, Cornell Conferences on Therapy, by the Macmillan Company.

DR. MCKEEN CATTELL: In opening the therapy conferences for the current academic year, I would like to call your attention to the fact that this represents the tenth year in which these conferences have been conducted. As you know, they are recorded; selected ones are published in the New York State Journal of Medicine and now also in the new journal, The American Journal of Medicine. Formerly it was possible for us to supply reprints, and these have been quite popular amongst the students and staff of the institution. I regret now, however, that through an arrangement with The Macmillan Company, who are publishing an annual volume of Cornell Conferences on Therapy, we have agreed to discontinue the distribution of reprints. I hope the journals are available to most of you.

I would like again to bring up a point which we do every year, namely, our wish and our hope that the students will participate fully in the discussions. As you know, the purpose of these conferences is to provide a medium for informal exchange of views between the various groups who are interested in the problems, and we are eager to have the students take part in the questions and comments. Often in the warmth of the discussion, there has been too much of a tendency to confine it among those in the front rows, but it will be our constant endeavor to have all of you participate.

The subject of the conference today is "The Dose of a Drug." We think this is an important topic. There are many points of information concerning it which are provided by experimental pharmacology, and these have not always been fully utilized in drug therapy. The discussion will be opened by Dr. Gold.

DR. HARRY GOLD: I am going to deal with a few matters which bear chiefly on problems of dosage. I believe that dosage is one of the very weak spots in drug therapy. A large proportion of the failures in drug therapy results not so much from the choice of the wrong drug, but from the use of the correct drug incorrectly. The fault lies in the dosage. The single dose is either too small or too large, or the dosage plan is, for one reason or another, unsuited for eliciting the full power of the drug for the particular situation. Examples will help to clear the points I wish to make. And right here I should like to state that any resemblance of this to a discussion on cardiology is purely accidental; I shall simply draw on some of the cardiac drugs for purposes of illustration. Whenever I see a patient in heart failure who I judge ought not to be in that state, and who proves the fact by quickly recovering when placed on an appropriate system of treatment, I almost invariably find that the patient has already received the drugs which are generally used for the treatment of heart failure; a salt-free diet

has been prescribed; digitalis has been given; and one or another diuretic has been in use. The failure to achieve satisfactory results was due to improper dosage; the salt intake was not sufficiently restricted; the amount of digitalis may not have been enough; and the system of administration of the diuretics was inadequate for the needs.

A few years ago, we published some studies advocating the use of an "average full dose" of digitoxin to be given at one time for digitalizing patients in heart failure. We encountered many obstacles to the acceptance of this idea. It was argued that the susceptibility of individuals differs, that a single average dose will not be enough for the tolerant patients, and will poison the more susceptible ones. You may have seen the paper which appeared August 1945, in the New York State Journal of Medicine, in which the author stated: "It is absurd to speak of digitalizing a patient on 1.25 mg. of digitoxin." He then added: "There never will be a single dose of digitoxin or any other glycoside which will uniformly digitalize all patients regardless of the age, the sex, the weight, or the general condition." The fact that such a statement was made indicates that some persons apparently believe that such a dose exists, namely, a dose which will digitalize all patients uniformly. Our attention was fixed on this statement by reason of the fact that this heresy was, by implication, ascribed to us. I have heard others voice disappointment with our proposed plan for the use of an "average full digitalizing dose" of digitoxin at one time, because in limited experiences it had failed to produce an expected degree of therapeutic results. It soon became clear to us that what troubles most people is the meaning of the term "average dose." We had a conference on digitoxin last year in which considerable time was spent in the endeavor to crystallize the meaning of the term "average dose."

The term "average dose" is very loosely used in therapeutics. We discovered, in that discussion, that the term is sometimes applied to the dose which produces the full effect in practically all cases. More often, it is applied to the dose which the "average physician" uses without regard for the origin of that usage. It is hardly necessary to point out that the "average dose" and the dose which the "average physician" prescribes are not the same.

In pharmacology, the term "average dose" has a fixed meaning. It is the dose which exerts a particular effect in 50 per cent of a population. When the end point is a lethal effect, it is referred to as the "average lethal dose" or the LD50.

The "average dose" in the pharmacological sense may also be determined in humans, and by substantially similar methods. Again, let us use an example to illustrate the method. If we were to start out to determine the "average dose" of digitalis which produces a T-wave change in the electrocardiogram, this is how we might proceed: We might start with 100 persons, we might give to each 0.1 Gm. digitalis, and twenty-four hours later we might take an electrocardiogram in order to see what percentage of the subjects showed a change. A month later, after the effects of this dose have disappeared, we might give the same group 0.2 Gm. digitalis, and again see what percentage showed an effect in the electrocardiogram twenty-four hours later. This procedure might be repeated at monthly intervals with increasing doses. At the end, we would have certain data, namely, a series of increasing doses and a corresponding series of increasing percentages of responses. If we then plot one against the other, we obtain a curve as illustrated in this diagram. (Fig. 1.) It is called a frequency distribution curve. This curve provides us with two kinds of information. It shows what the "average dose" is to produce the particular effect, namely, that

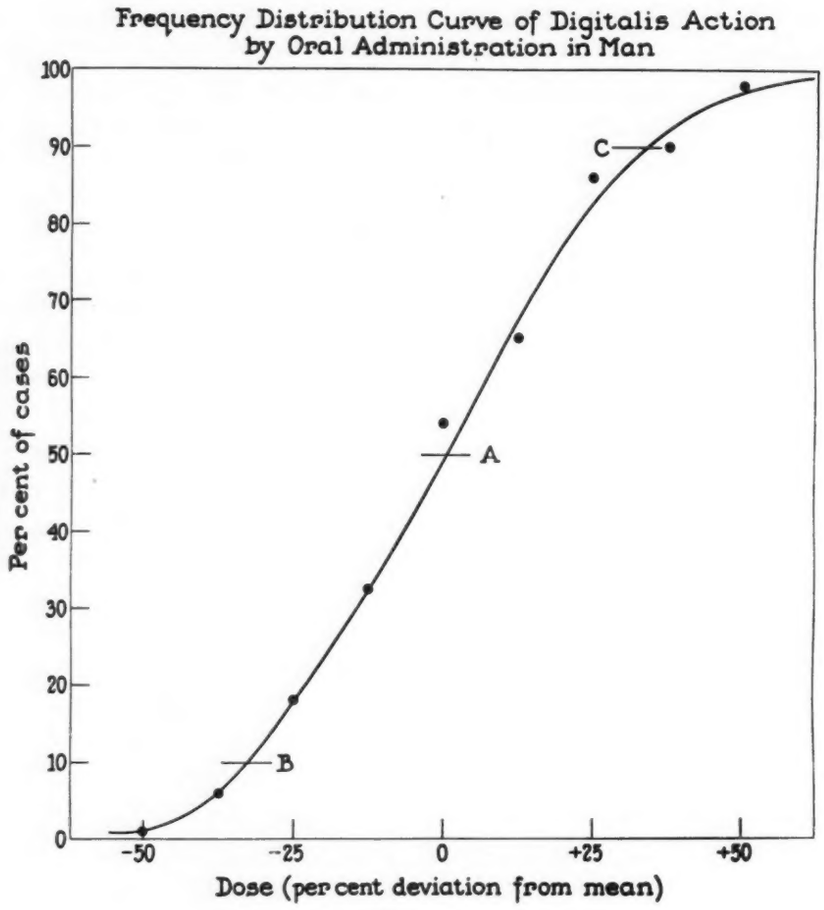


FIG. 1.

dose which produces the effect in one-half of the population. The shape, the steepness, and the length of the curve also show us the range of variability in the sensitiveness of the human population with respect to the particular drug and particular effect.

Such a curve gives us additional information. It tells us how useful an "average dose" for a given drug is likely to be. If the curve happens to be a fairly short and steep one, it shows that the sensitivity of one person differs very little from that of another, and that if, in such a case, the "average dose" were to be given to all, the results would be very satisfactory since some would show the precise therapeutic response, and the remainder, only a little less or a little more than the exact therapeutic end-point. On the other hand, if the curve is fairly long and flat, it shows that the sensitivity of one person differs greatly from that of another; the scatter may be very wide; and the limits so extreme that one patient may require ten or twenty times as much as another to produce the same effect.

If a drug were to show such a long and flat frequency distribution curve, the "average dose" for this drug would not be very useful. One would have to start therapy with much less than the average dose in order to avoid poisoning the more susceptible members of the population.

We have determined the curve for digitalis. It is fairly steep and short. If 100 persons were to receive the "average dose," as you see on the diagram, about 75 of them would show the following results: Some, would show exactly the desired response; some, responses from doses down 25 per cent less; and some, responses from doses up

to 25 per cent more. Almost all are included in the "average dose" ±50 per cent. Since we know that the end-point in digitalization is not very precise, such variations would, for the most part, escape detection, and even the occasional extremes would not cause serious poisoning. In the case of digitoxin, therefore, the "average full digitalizing dose" is a most useful unit of dosage.

Well, we know how these matters stand in the case of digitoxin, but for the vast majority of drugs in common use we do not have a frequency distribution curve in humans, and we do not know what the "average dose" is. Consider the case of epinephrine for the treatment of an attack of bronchial asthma. Where on the curve (see Fig. 1) does the usual dose stand? If the usual dose which is employed should happen to stand down at the point B, it would mean that it is too small, and that with the usual dose, there may be an unnecessarily large number of failures to produce the effect we are after. On the contrary, if the dose which we commonly employ should happen to stand at point C on the curve, it might indicate a dosage level in which we are obtaining an unnecessarily large number of cases of poisoning or undesirable side-effects. The fact remains that we do not know the "average dose" of epinephrine. Nor do we know the "average dose" of physostigmine for the treatment of abdominal distention, the "average dose" of morphine for pain, the "average dose" of phenobarbital for sedation, or of castor oil or magnesium sulfate for cathartic action. Here is a perfectly simple pharmacological conception which is readily accessible to application in patients, but in the clinic we continue to trundle along in the matter of dosage on more or less accidental and empirical experiences. So much for the "average dose."

The next point I should like to discuss is the dosage plan. There are essentially two types of dosage plans; one, the cumulative dosage plan; and the other, the non-cumulative dosage plan. By the cumulative plan, we mean a plan of dosage which involves giving a small dose at the beginning and repeating at such intervals as to build up a concentration in the blood or the tissues adequate to produce the therapeutic effects. This method is used in the interest of safety. If the single full dose is unknown or is dangerous, as it is in most cases, the full dose is built up by steps, each of which in itself causes no harm or no serious toxicity. The ideal system involves knowing when the peak effect of any dose is reached. If the peak is reached in two hours after an oral dose, let us say, the interval between doses should be two hours; if the peak effect is reached in six hours, then the interval between the fractions should be six hours. The use of quinidine is a good example. If the objective is to bring to an end an attack of auricular fibrillation or ventricular tachycardia, one should start with a small dose, say 5 or 10 gr., and since it is known that the peak effect is reached in about two to three hours, repeat the dose at such intervals until enough has accumulated to produce the desired effect. The total amount of the drug does not matter. There can be no talk of failures unless such a cumulative system has been put into operation with the end-points being the therapeutic results or minor toxic symptoms. Picrotoxin in the treatment of barbiturate poisoning is another good example. In such a case we often do not know the true depth of the narcosis or the dose of the barbiturate. We start with a small intravenous dose which could not do anybody any harm. To the peak effect of this, which is reached in about ten or fifteen minutes we add the next dose, and so we continue by steps until a concentration is reached which begins to produce therapeutic results. So much for the cumulative system.

The non-cumulative plan is just the reverse. It involves giving a single effective

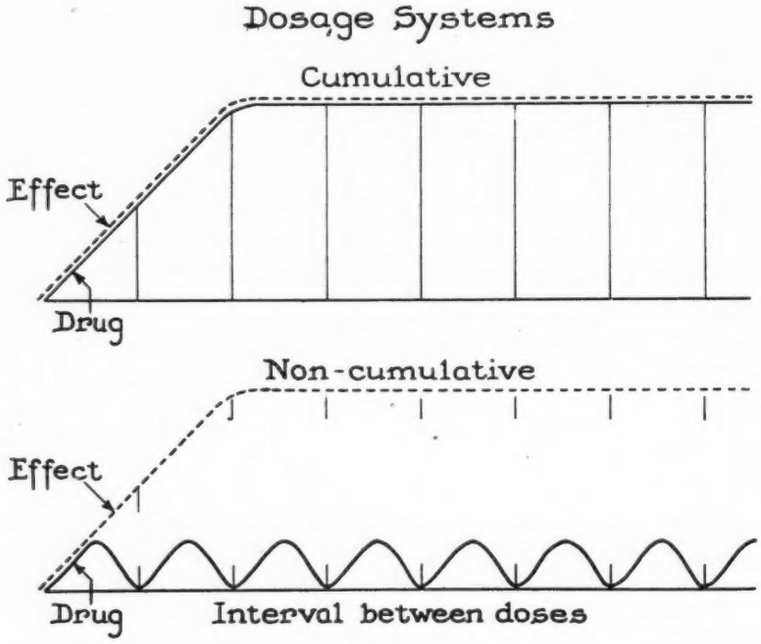


FIG. 2.

dose, but repeating it at such intervals as will prevent raising the concentration in the blood or the body tissues. Here the results may be cumulative, but the drug is not. The use of the mercurial diuretics is a good example. If the loss of weight of the patient with edema is the measure of the therapeutic effect, the plan is to repeat the dose at such intervals as to produce progressive loss of weight, but without significant increase in the concentration of the mercurial in the body above that of the first dose. Since these drugs are excreted in about twenty-four hours, the repetition of the dose at daily intervals provides a suitable non-cumulative plan.

These diagrams (Fig. 2) illustrate the two systems of dosage which apply to the majority of drugs. One is the system of rising steps, each in itself without danger; and the other is a system of complete curves of absorption and elimination. As I have indicated, in order to put these mechanisms into most effective operation, we have to have several bits of information. We should know about how quickly the drug is absorbed, the time it takes to reach a peak effect, and something about the speed of its elimination or duration of action. In this connection, there is the fact that cumulation is a self-limiting process for the majority of drugs. If one gives a patient a dose of 1 Gm. of sodium bromide every day, one finds that the blood concentration of bromide begins to rise, and continues to do so for two or three weeks. The blood concentration curve then levels off even though the same daily dose is continued indefinitely; an equilibrium is reached between the daily dose and daily excretion. In the case of digitalis, we see the same phenomenon at work, although we detect it in a different way. If a patient with auricular fibrillation and an apex rate of 140, receives 0.2 Gm. of digitalis every day, the apex rate begins to slow; it gradually declines to a level of about seventy a minute below which it may not go even though the same daily dose is continued indefinitely. First there was the period of cumulation, then the period when cumulation no longer occurred.

The duration of the period of cumulation differs for different drugs. In the case of digitalis, a fixed daily dose may show cumulation for two to three weeks before the

effect levels off. One cannot be sure that the patient will not become toxic, when using a fixed daily dose, unless it has been used for about three weeks in the case of digitalis. On the contrary, in the case of quinidine, cumulation ceases in about three or four days; if a patient receives, let us say, 1 Gm. of quinidine every day, the second day may show greater effects than the first, and the third may show greater effects than the second, but after the fourth day the effects are likely to level off and no further cumulation is apt to occur after that. These periods are not fixed with precision, but it is of the order of four or five days for quinidine and of the order of two to three weeks for digitalis.

There is still another point, namely, that the level at which cumulation ceases depends on the size of the daily dose. By way of illustration, cumulation of digitalis with a daily dose of 0.1 Gm. may level off at an apex rate of 100 a minute, while with a daily dose of 0.2 Gm., at an apex rate of 80. So also, in the case of the bromides cumulation ceases at a lower blood concentration of bromide when the daily dose is 1 Gm. than when it is 2 Gm.

There is no doubt that the points which I have discussed as requiring attention in rational systems of dosage play a part in the use of drugs as practiced at the present time. I have little doubt that the doses which are prescribed in the case of some drugs are actually the "average doses." Cumulative and non-cumulative systems are at work in dosage plans that are commonly used, but I am inclined to think that their operation is more by accident than design. For that reason, we find cumulative systems employed in cases where non-cumulative systems would give immeasurably better results and vice versa.

To find illustrations, one does not have to go very far. It is one of the most common of experiences to encounter patients receiving, let us say, 0.3 Gm. of quinidine three times a day for weeks on end for a particular disorder of rhythm without producing any beneficial effects; one could have predicted the failure at the end of the fourth or fifth day. Since the system did not provide enough cumulation in the first four or five days, there remained nothing to do but to raise the single doses or to give fractions at shorter intervals during the day. You will find several reports in the literature, for example, pointing to the percentage of cases with auricular fibrillation in which quinidine succeeded in establishing a normal rhythm. What meaning have these percentages? If you will examine these reports you will find that a rigid dosage was used for all. That is no way to find out how effective quinidine can be.

Morphine is often given by hypodermic injection in urgent situations at intervals of ten or fifteen minutes. There can be no meaning in such intervals since so little of the first dose is absorbed, the peak effect of the first dose being reached in from thirty to forty-five minutes, or in some cases longer. I have seen prostigmine used for abdominal distention in doses at intervals of six or more hours. The first dose produced no effects, and neither did the others. The effects wear off within about two hours. Here, then, is a system of dosage which could by no possibility elicit the therapeutic effects of this drug. And when I hear it said that a particular drug was without value in the case in question, I ask at once, how do you know? Was it used in such a manner as to make sure that there was here a case which could not respond favorably? The mercurial diuretics are recommended in the textbooks to be given at 4-day intervals. The mercurial is excreted within about twenty-four hours. To spread the interval to four days, simply allows a long period to elapse in which the patient receives no treatment, and in this time the condition remains stationary or deteriorates. It serves no pur-

pose other than to prolong the period of recovery from the heart failure.

Mapharsen in the treatment of syphilis is another case which requires attention from the standpoint of the present discussion. A dose is almost completely excreted in two to three days, and while there are some advocates of rapid methods which appear to take this into account, the most popular dosage plans call for only one injection a week.

The cumulative and non-cumulative systems of dosage do not exhaust the problems of dosage. There are situations in which a more or less fixed plan of dosage needs to be used without adjustments for the needs of the particular individual. These are cases in which precise therapeutic end-points or minor toxic end-points are not available as a guide to the adjustment in dosage. A good example is the use of digitalis in the heart failure of rheumatic active carditis. Here the therapeutic results are often indecisive and if one attempts to increase the concentration by the cumulative method, one frequently encounters troublesome and sometimes dangerous toxic symptoms. It is, therefore, best in such a case to adopt a fixed system of dosage with the highest prospects of therapeutic benefits and lowest liability of producing toxic effects, and to use that system in all without attempting to increase the dose to meet the needs of the particular case.

Therapeutic effects and minor toxic symptoms are the chief guides to adjustment of dosage in the cumulative systems. There are, however, cases in which special devices are used for that purpose. For example, in the case of insulin in diabetes, the adjustment of dosage depends to a large degree on the amount of sugar which appears in the urine rather than on any specific effects on the patient, although the latter factor is taken into account. Another specific method for adjustment of dosage is shown by the case of Hemophilus influenzae rabbit serum. Here the dosage may be determined by the immune properties developed in the patient's serum or the immunity reaction after an intracutaneous injection of the specific antigen.

I do not believe that we have the time to go into the details of these special problems in this conference.

Dr. McKeen Cattell: I would like to make one remark in relation to your curve, Dr. Gold, which I think may help to clarify the principle which determines the maximum extent of cumulation over a period of time. A cumulation curve, such as you drew, with a maximum or ceiling effect, represents the cumulation of the effects from the single doses, and is determined by adding the separate curves for each point of time. Thus, one has a whole series of curves of drug effect and the actual cumulation is measured by the sum of the effect of each of the doses at any point on the time axis. Once the point is reached at which the effect from the first dose disappears, then the added effect will be equal to that which is dissipated, and the curve will level off. So the explanation of cumulation from repeated doses is not obscure, but involves the knowledge of a very simple pharmacologic principle in relation to the persistence of the effect of a drug.

Dr. Cary Eggleston: There were two items in Dr. Gold's discussion that I thought deserve comment. Dr. Gold discussed the term "average dose." I would like to say a word about that. In the United States Pharmacopoeia the term "average dose" is found in the case of almost every drug. Dr. Gold defined "average dose" for you here in the pharmacologic sense. The Pharmacopoeial definition of "average dose" is quite another thing, and I think you may be misled if you do not understand the difference between those two uses of that term. The Pharmacopoeia assigns a dose on the basis of conference between a considerable group of men supposed to be best informed in the case of the particular agent, and on that

basis the committee attempts to pick out a dose which may be stated as the "average dose." It is merely a rough guide to the practicing physician, so that he will have some idea as to the single dose with which he should start the treatment of the patient. I think that the Pharmacopoeial Committee on Therapeutics realizes that the term "average dose" is misused; in fact, I think that they realize that it is an unfair statement, but the physician must have some starting point.

DR. CATTELL: Isn't it usually a minimal dose?

DR. EGGLESTON: It is usually a dose which is, par excellence, safe; safe in the sense that it will do no harm. It may not be safe because it may be totally inadequate to accomplish the purpose, and by the time one has discovered this it may be too late to remedy the situation, but the Pharmacopoeia cannot deal with all the problems in a statement such as this. That is all I wanted to say: Keep those two thoughts separate in your minds. The Pharmacopoeial "average dose" is a statement of what is commonly found to be safe, and, presumptively, what a great many physicians believe is more or less effective when repeated. Dr. Gold's use of "average dose" is much more scientific but unfortunately it is one which has not come into vogue as yet with the exception of a few isolated drugs, and those drugs are usually ones with more or less simple actions and reasonably clear-cut end-points for judging their actions.

Dr. Gold also spoke of the question of cumulation in the use of the mercurial diuretics. I don't want to seem to be critical, but I think, possibly, there is another idea there which he omitted to mention, namely, that at times we must consider cumulation of effect as well as cumulation of drug. We know that the mercurial diuretics available to us today do not remain long within the body. Dr. Gold has stated the approximate period as about twenty-four hours. While it is a fact that, within twenty-four hours, virtually all of the mercurial has been eliminated from the body, there is also the fact that it is often highly undesirable and at times productive of discomfort to the patient to produce dehydration too rapidly. That, perhaps, rather than the danger of toxicity, is one of the explanations for the frequent use of the mercurial diuretics at longer intervals.

DR. CATTELL: I wonder if we might have a few words from Dr. Stewart while we are on this general topic, and then perhaps turn to Dr. Gold for a response.

DR. HAROLD G. STEWART: The diagram that Dr. Gold drew, of the T-wave effect and dosage of digitalis, does not seem to me to have a great deal of relevancy to the therapeutic use of digitalis. I think almost everybody is agreed that you cannot look at a record of a patient who has had digitalis and tell from the T-waves how much digitalis that patient has had. From a therapeutic point of view, I think we do not want the students to carry away the notion that you can look at a record and tell whether a patient is adequately digitalized or not. It may be that if you observed one patient, and repeatedly digitalized him, after allowing time for excretion, that patient, on a certain amount of digitalis might exhibit somewhere near the same kind of T-wave changes; but you cannot predict what another patient would do with the same or another amount of digitalis in the way of T-wave changes. Consequently, we cannot use T-wave effects as a guide to whether we are getting an adequate therapeutic effect from digitalis or not.

To come back to the word "average" again, it seems too bad that there has seeped into the literature a sense that was not made clearly in Dr. Gold's papers about this; it is interpreted by everybody that I have talked to, to mean that if you give 1.2 mg. of digi-

taline Nativelle you digitalize the patient. That is the current notion. I think harm to progress in digitalis therapy has been done by the prevalence of this notion which is now current. As a matter of fact, we see patients now less well digitalized than we did five or six years ago before this notion got around that one could do it with these small amounts. I think in the experience of most people, except Dr. Gold, it takes larger amounts than 1.2 mg. to give adequate digitalization. In our experience here it is somewhere between 1.8 and 2 mg. If 1.2 mg. is the "average" digitalizing dose, it is very unusual that we do not see patients in our experience in whom this amount achieves digitalization.

DR. CATTELL: I am sure there is no disagreement with what Dr. Stewart said with reference to the wide variability among patients in their response to digitalis and the consequent impossibility of using the T-wave or any other criterion to establish the quantity of digitalis administered. It is precisely for this reason that it is so important to have information about individual variability in the population to be treated. We then have advance information on the probability of the average or any other dose giving the desired therapeutic effect, or of its being too large or too small. This is a point of great practical importance which has not been given the attention it deserves. Thus, Dr. Gold's average dose of 1.2 mg. of digitoxin becomes more informative, when at the same time he is able to tell us in what proportion of patients it is ineffective and in what proportion it gives rise to toxic symptoms.

Nothing in what I have just said detracts from the evidence obtained by the comparison of the effects of repeated doses in the same patient. By such means which eliminate the factor of individual variability, it has been established that a definite dosage-response relationship holds and that the T-wave changes correspond quantitatively to the therapeutic actions.

DR. EGGLESTON: May I raise a point? I quite agree that the studies by Dr. Gold in the attempted establishment of an "average dose" of digitoxin were exceedingly well thought out and very cautiously investigated. I think the use of the term "average dose" without specific definition, conveys the wrong idea to the practicing physician. He certainly generally expects that when he gives the dose set by Dr. Gold, that dose which is quite definitely established as the average, meaning that dose which will produce a given effect in 50 per cent of instances, that it is the therapeutic dose of digitalis. Perhaps it is an unfortunate choice of a word. I do not know what word could have been chosen, but I think that Dr. Stewart is right, namely, that it does convey an erroneous impression. It is all right among our own students here because they understand what is meant by that, but the medical public at large does not.

DR. CATTELL: Do you not still think that if you have the information about the "average dose," it represents the most desirable starting dose?

DR. EGGLESTON: Yes, probably it does. For that matter, I could not help thinking when Dr. Stewart was talking here, and I hope he will pardon me for this remark, that for many years it was routine in this Hospital to give each cardiac patient admitted to the Hospital, without other consideration than that he had not recently been digitalized, 1.8 Gm. of powdered leaf. That is precisely the same principle as Dr. Gold's. We found that 1.8 Gm. of powdered leaf in divided doses was reasonably effective in controlling the majority of the symptoms of congestive heart failure. We were able to save the patients several days of hospitalization by that, and what is still more important, many hours of unnecessary discomfort were saved. However, I think you

ought all to understand that, precise as some procedures are in therapy, there is still the problem that you cannot get away from, namely, that of individual variation of the patient.

DR. CATTELL: If it is safe, may it not be desirable to give more than the average dose which takes care of 50 per cent of the cases? Provided there are no side actions of importance, it would be desirable to give that dose which might encompass the largest number of cases. That can be done with many drugs.

DR. STEWART: I think then, that should be called partial digitalization or some implication of that given.

DR. CATTELL: Now I want to give Dr. Gold a chance to reply.

DR. GOLD: The discussion here establishes the wisdom of the committee in choosing this topic for an airing in the conference today. It just goes to show how little this whole matter is understood. From the standpoint of the Pharmacopoeia, Dr. Eggleston, I would recommend that you and I form a committee of two to urge the Pharmacopoeia to abandon the term "average dose," and substitute the term "the dose" or the "usual dose."

DR. EGGLESTON: That might be well.

DR. GOLD: There is no reason why the Pharmacopoeia, which is so highly scientific in most of its performances, should continue to carry along the term "average" as applied to dosage, in a completely unscientific sense, having it mean not the "average dose," but the dose which the "average physician" prescribes. Please consider the resistance which we are encountering right here at this conference to our endeavor to place the term "average dose" in its proper light. Dr. Stewart and Dr. Eggleston state that it is a source of confusion to physicians because they believe that the term implies that the full effects will be produced in every patient if that dose is given. Perhaps, some do believe that, but I have confidence that the majority of physicians do not believe that. There is no more mystery about the term "average" as applied to the dosage of a drug than there is to that term applied to the physician's daily income or to the size of men's heads. Clearly, there is need for more education on the subject and for calling attention to the fact that the "average dose" can only produce the desired therapeutic effect in a proportion of the population, a larger proportion in the case of some drugs than of others. The remainder may do with less than the "average dose" or may require more than the "average dose." It is incredible to me that anyone would question the need of determining the true position of the "average dose" in the dosage scale as a basis for deciding what dose should be used as the starting point for therapy. As Dr. Cattell intimated, if it happens to be a drug in which the therapeutic and toxic effects are close, it may be necessary to start treatment in any particular case with less than the "average dose," but if the drug happens to be one in which therapeutic and toxic effects are far apart, treatment may be started in all patients with more than the "average dose." For example, we might determine the "average dose" of penicillin which cures pneumonia, but since penicillin is non-toxic, it would be desirable to treat all patients not with the "average dose," but with a much larger amount, an amount which would cure not 50 per cent of the population, but as close as possible to 100 per cent of the population.

As to the specific example of digitoxin, we published a study in which the term "average full-dose-method of digitalization" was used, and the experience was described in which that turned out to be 1.2 mg. given at one time. Our papers clearly state, and the term "average" clearly implies, that some require more, while others can do with less. Dr. Stewart appears to be taking issue with it, and it is not clear to me whether the

objection is to the conception of the "average dose," or only to the 1.2 mg., or to both.

Since Dr. Stewart stated that "in the experience of most people, except Dr. Gold, it takes larger amounts than 1.2 mg. to give adequate digitalization," I should call your attention to the paper by Stroud and Vander Veer in 1937 in which they found that from 1.2 to 2.0 mg. of digitoxin was necessary for full digitalization when the drug was given over a period of five or six days. There is also the recent paper by Katz and Wise in the American Heart Journal of August, 1945, in which they confirm our results and state that "digitaline 'Nativelle' in 1.2 mg. dosage . . . . . would appear to provide safe, effective, single-dose digitalization in undigitalized patients." I believe I know why Dr. Stewart is having so much difficulty with the 1.2 mg. dose. I surmise that he fails to give it at one time, that he does not use the control period which eliminates the effects of rest in bed, as was done in the method by which the 1.2 mg. value was established, and that his experience may not embrace a sufficient variety of grades of failure, from the very mild to the very severe ones. Not dealing with an "average" population, he may fail to observe the expected results of an "average dose."

Dr. Eggleston, your point about the mercurial diuretics is well taken. We all encounter the unpleasant effects of excessive diuresis; and in a case in which it has occurred after the first dose, we have to wait a few days until the patient recovers from them. However, our solution to the problem is not the one you suggest, namely, to spread the interval between injections; it is rather to keep the interval unchanged but reduce the dose. This usually results in a continuous course of improvement or cumulation of effects without the drastic disturbance from excessive single doses given at intervals of four days.

DR. EGGLESTON: I was not discussing the use of the mercurials. I agree with you that often the individual dose should be smaller.

DR. GOLD: I stated at the beginning that any resemblance of this conference to a discussion on cardiology was purely accidental. I used the frequency distribution curve which we determined for the effect of digitalis on the T-wave of the electrocardiogram as an example of the method which may be used for establishing the "average dose" of a drug and the range of variability in the response of the human population. But since Dr. Stewart has broadened the discussion, I may state that I agree with him that there is no necessary relationship between the T-wave effects of digitalis and its effects in heart failure.

DR. CATTELL: Would you admit that different systems may show different degrees of susceptibility?

DR. GOLD: Indeed I do agree. In point of fact, on the average, it takes about three times as much digitalis to bring about the full therapeutic effects in heart failure as to produce changes in the T-wave, and there are some patients who show negligible changes in the T-wave with doses of the drug sufficient to control heart failure, while others may show advanced T-wave changes with doses of the drug which cause negligible effects in heart failure.

DR. CATTELL: Would you think it safe to apply the frequency distribution curve obtained with the T-wave to the case of treating heart failure?

DR. GOLD: On theoretical grounds, I would hesitate to do so. It could be that the range of variation in the susceptibility of humans from the standpoint of the cure of heart failure might be quite different from that for the T-wave response. The two curves might have different slopes and different lengths. However, as you have already intimated, in the experiments with the T-wave, we found that the "average dose" ± 25 per cent includes about three-fourths

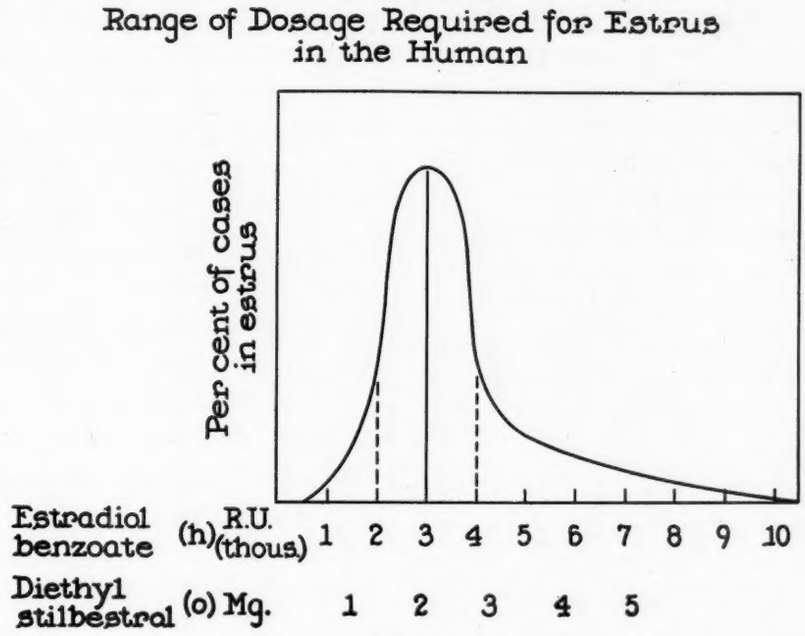


FIG. 3.

of the population, and in our experiments with heart failure and auricular fibrillation, the single dose of 1.2 mg. of digitoxin given at one time, as well as the 0.2 mg. given daily for maintenance, produce satisfactory digitalization and maintenance respectively, also in approximately three-fourths of the population. The results, therefore, suggest that in the case of these two responses to digitoxin, the two curves happen to be similar.

DR. EPHRAIM SHORR: Everything that Dr. Gold has said about dosage in cardiology has occurred to every one of us who, in our respective fields, have been concerned with therapeutic misinterpretations of the same character; and I am sure that each one of us could cite example after example that fit each of the fundamental therapeutic principles which Dr. Gold has so well laid down. The field of endocrinology is probably surrounded by more therapeutic pitfalls than almost any other that I could name. Let us, for example, consider the use of estrogens. We have been provided with a number of potent estrogenic preparations which are standardized in terms of rat units or international units. There is an average dosage suggested by the Pharmacopoeia. This average dosage is arrived at in the same way as the average dose of other drugs and is equally useless as a guide for therapy. The bio-assay of these materials is carried out on the same principles as that for other drugs, namely, a 50 per cent response. The chief purpose of this assay is to insure that estrogenic preparations meet standard requirements. However, their direct application to therapy in the human must, in order to be successful, be guided by the fundamental therapeutic principles which hold for any other drug and by the recognition that gross individual variations in responsiveness exist in the human population as in the rat colony on which the bio-assays have been made. It is, therefore, essential that we have some objective index analogous to the T-wave in the electrocardiogram to serve as a guide post. For the estrogenic hormones this is provided by the vaginal smear which undergoes specific cytological alterations under the influence of estrogens, its end-point being a fully cornified smear. When one uses this index as a basis for replacement therapy

with estrogenic hormones one finds the expected variation in dosage requirements from patient to patient. This range of dosage is shown semi-diagrammatically in Figure 3. It is, of course, possible to select a range of dosage which will put approximately 50 per cent of patients in full estrus; however, this dose will be excessive for a certain percentage of patients and inadequate for another group. This circumstance is completely analogous to the response to the average digitalizing dose of digitoxin as Dr. Gold has pointed out.

A second variable in the use of the estrogenic hormones is presented by variations in the intervals between injections. Thus, you may get entirely different results using any given total dose depending upon whether the whole amount is given at wide intervals, or in divided doses given daily. By far the most efficient utilization of the hormone occurs when it is given daily. Finally, there is the matter of the cumulative effect of estrogens. If a dose is inadequate to achieve a desired effect it may be given indefinitely without fulfilling its purpose.

I am sure that these three examples which illustrate the relevance of Dr. Gold's discussion of the fundamental principles which should guide therapy could be multiplied indefinitely, not only in the field of endocrine therapy, but in virtually all of the medical disciplines.

Summary

Dr. Gold: The discussion in the conference this afternoon centered on problems of dosage. The principles were explored and illustrated by examples from a wide variety of drugs. There are two systems of dosage by which drugs are administered, the cumulative and the non-cumulative systems, and for their most effective application, use must be made of pharmacologic facts relating to speed of absorption and elimination. The mechanisms of these systems were described. The significance of the "average dose" was discussed, and a method for establishing the "average dose" in humans was outlined. The "average dose" of digitalis received special attention. It was stated by one participant that the "average dose" with respect to the effect of digitalis on the T-waves of the electrocardiogram bears no relation to the average therapeutic dose of the drug, while others presented evidence indicating a close correlation between the two types of endpoints.

It was stated that the position of the "average dose" is not known in the case of most drugs, and that the term "average dose" is incorrectly applied to the dose which the "average physician" prescribes. The application of the principles of dosage was considered in relation to such common therapeutic agents as digitalis, epinephrine, neostigmine, phenobarbital, picrotoxin, morphine, quinidine, mercurial diuretics and estrogenic hormones. It was pointed out that if physicians were to make more systematic use of the basic principles of dosage plans, the efficacy of drug therapy would greatly increase.

Clinico-pathological Conference

Blood Dyscrasia with Cardiac Complications*

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., of weekly clinico-pathological conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, E. W., was a sixty-one-year old white divorced bank guard, who entered the Barnes Hospital for the first time on October 9, 1946, complaining of shortness of breath. The family history was non-contributory. The past history revealed that the patient had had pneumonia in 1914 without complications. He had had no other serious illnesses, and the systemic review was negative.

Approximately one year before entry, the patient was told by friends that his eyes were becoming more prominent and from that time on exophthalmos had increased. Shortly after the prominence of his eyes was first noted, the patient became more nervous and developed a slight tremor of his hands. About four and one-half months prior to admission, he became dyspneic for the first time on exertion; dyspnea increased rapidly so that soon it was present when the patient was at rest. Orthopnea and a persistent, non-productive cough occurred. Concomitantly the patient became aware of masses in his neck and in the axillae, and he entered the Washington University Clinics.

There it was recorded that he did not look particularly ill. A patchy maculopapular erythematous eruption was noted over the chest and inguinal regions. There was generalized lymphadenopathy; the nodes varied from ½ to 2 cm. in diameter and were discrete, firm and non-tender. The eyes were prominent. The pupils reacted to light and accommodation and extra-ocular movements were normal. The optic fundi showed only moderate retinal sclerosis; no hemorrhages or exudates were present. The tonsils were enlarged but did not appear inflamed. The lungs were clear to percussion and auscultation. The left border of cardiac dullness was 9 cm. to the left of the midsternal line in the fifth interspace. The rhythm was regular, the sounds were of good quality and there were no murmurs. The spleen was palpable 10 cm. below the left costal margin but the liver edge could not be felt. The prostate was twice its normal size. There was no clubbing or edema and the neurologic examination was within normal limits. Laboratory studies included a normal red blood count and hemoglobin. The white cell count was 173,550 and the differential count showed 1 per cent stab form, 3 per cent segmented forms, and 96 per cent lymphocytes; 6 per cent of the lymphocytes were immature. A chest film was read as follows: "The cardiac silhouette is within normal limits. The hilar markings are prominent on both sides. There is pulmonary infiltration in the second and third anterior interspaces on the right and to a lesser extent along the descending bronchi. X-ray diagnosis: peribronchial infiltration of an indeterminate nature."

A diagnosis of chronic lymphatic leukemia was made and from June 26, 1946, to July 31, 1946, the patient was given

* From the Departments of Internal Medicine and Pathology, Washington University School of Medicine and the Barnes Hospital, St. Louis, Missouri.

seventeen x-ray exposures. He was then followed in the Anemia Clinic where examination revealed that the spleen and lymph nodes were reduced in size. On September 17, 1946, the following laboratory data were recorded: red blood count, 4,480,000; hemoglobin, 13.2 Gm.; reticulocyte count, 3 per cent; white cell count, 37,400; differential count: 1 per cent eosinophiles, 1 per cent segmented forms, 96 per cent lymphocytes, and 2 per cent monocytes; platelets, 270,000.

During the course of x-ray therapy most of the patient's symptoms had improved considerably but his appetite became poorer. He felt fairly well until one week prior to entry when he again became markedly short of breath and developed nausea, vomiting and diarrhea. Six days before admission he complained of pain in the left chest substernally, associated with marked orthopnea. Three days before admission edema of the legs appeared. Because of the persistence of these symptoms he was admitted to the hospital.

No temperature reading was recorded and the pulse was not obtainable. The respirations were 32 per minute and shallow, and the blood pressure was 85/65. The patient was critically ill and sat on the edge of the bed gasping for air. The arms and legs were cold and clammy and there was cyanosis of the lips and of the finger nail beds. Moderate exophthalmos and lid lag were noted. The mucous membranes of the mouth were cyanotic. The tongue protruded in the midline without tremor. There was marked distention of the neck veins. The trachea was in the midline; the thyroid was normal in size but a small nodule was palpated in each lobe. There was dullness to percussion at the base of the right lung and over this area tactile fremitus, breath sounds and spoken voice were diminished. No râles were heard and the remainder of the lung fields was clear to percussion and auscultation. The cardiac impulse could not be seen or felt and no heart sounds were audible. The heart was enormously enlarged; right border dullness was 3 cm. from the midsternal line in the second interspace, 5 cm. in the third interspace, 9 cm. in the fourth interspace, and 13 cm. in the fifth interspace. The left border of cardiac dullness was 6 cm. to the left of the midsternal line in the second interspace, 8 cm. in the third, 12 cm. in the fourth, and 16 cm. in the fifth interspace. The spleen was palpable 7 cm. below the left costal margin, and the liver 11 cm. below the right costal margin. There was 4+ pitting edema of the feet and lower legs.

The laboratory findings were as follows: Red cell count, 4,550,000; white cell count, 96,000; differential count: 8 per cent segmented forms, 92 per cent lymphocytes. Blood Kahn reaction: negative. Venous pressure: 310 mm. NaCl. Circulation (arm to tongue with Decholin): 78 seconds. Roentgenogram of the chest: "The cardiac silhouette is enlarged to the right and left. The hilar shadows are prominent and there is fluid in the right pleural cavity." An electrocardiogram revealed low voltage in leads I, II and III, moderate slurring of all ventricular complexes, inversion of the principal component in I with upright principal components in II and III. There was a Q wave in CF_{IV}. Interpretation: "right bundle branch block and low voltage."

Immediately on entry the patient was given oxygen through a positive pressure mask and his cyanosis was relieved; however, he could not tolerate the mask and it had to be removed. Because the signs were thought to be those of cardiac tamponade, pericardial paracentesis was attempted; a No. 18 needle was introduced in the left fifth interspace at the outer border of cardiac dullness. No resistance was met and after the needle had penetrated 4 cm. blood was easily aspirated. Fifty cc. were withdrawn and the procedure was terminated. The

patient tolerated it well. The count on the bloody fluid obtained revealed 4,810,000 red cells, 13 Gm. of hemoglobin and 80,600 white cells. As a result of these findings it was concluded that the patient had acute cardiac dilatation rather than cardiac tamponade and he was given 1.6 mg. of lanatoside C intravenously over a period of five minutes. Shortly after the injection was completed, he slipped backward from his sitting position, had a mild generalized convulsion, took a few deep gasps for breath and expired. Death occurred approximately one and one-half hours after admission.

CLINICAL DISCUSSION

DR. HARRY L. ALEXANDER: Two features of this case deserve discussion, namely, the hematologic diagnosis and the etiology of the heart disease. Because the patient died so soon after admission to the hospital, the data are somewhat limited. Dr. Moore, would you comment on the hematologic problem?

DR. CARL V. MOORE: This patient probably had chronic lymphatic leukemia. I qualify my statement because neither a lymph node biopsy nor a bone marrow aspiration was recorded, and rarely a leukemoid reaction, characterized by a great increase in cells of the lymphatic series, may result from a chronic infection such as tuberculosis or from wide-spread neoplastic disease.

DR. ALEXANDER: Could lymphosarcoma be associated with a peripheral blood picture such as that seen in this case?

DR. C. V. MOORE: Yes, but I believe it can be excluded here. As you know, there is considerable interest among members of the hematologic division in the occurrence in lymphosarcoma of a peripheral blood picture simulating that of lymphatic leukemia. Not one of the members of the division who examined this patient's smear thought that the cells were those of lymphosarcoma.

DR. ALEXANDER: Is it true that x-ray therapy may lead to the development of a leukemoid peripheral blood picture in lymphosarcoma?

DR. C. V. MOORE: Yes.

DR. ALEXANDER: Does pulmonary infiltration occur in leukemia?

DR. ALFRED GOLDMAN: It is seen not infrequently. I do not believe that the x-ray findings in this case are necessarily due to infiltration with leukemic cells however; they may have represented the changes of low grade pneumonitis.

DR. ALEXANDER: Is it possible to distinguish Hodgkin's disease from leukemia by the nature of the pulmonary infiltration?

DR. C. V. MOORE: I do not think so. In general, approximately one-third of patients with lymphosarcoma, Hodgkin's disease, and chronic lymphatic leukemia have some form of pulmonary involvement equally divided between pulmonary infiltration, mediastinal adenopathy and pleural effusion. Given one of these changes, however, I do not believe that the correct hematologic diagnosis can be made on the basis of the x-ray film.

DR. ALEXANDER: This patient received seventeen x-ray treatments and it was noted that the size of the spleen diminished. Are the cells of lymphatic leukemia quite sensitive to roentgenotherapy?

DR. EDWARD H. REINHARD: They are definitely radio-sensitive although not to as great a degree as the cells of leukosarcoma.

DR. ALEXANDER: Apparently the pulmonary infiltration cleared after x-ray therapy. Would you have expected the spleen to return to normal size?

DR. REINHARD: Usually there is a greater decrease in the size of the spleen than was noted in this case. However, the response to x-ray therapy depends to a considerable extent on the duration of splenic enlarge-

ment; the longer the spleen has been enlarged, the less likely is there to be a good response to x-ray therapy.

DR. DONALD S. BOTTOM: It should be pointed out that this patient did not receive x-ray therapy directly to the spleen but only to the inguinal, axillary and cervical nodes. Frequently, however, the spleen is reduced in size even though radiation is not directed toward it.

DR. ALEXANDER: If x-ray therapy was directed primarily to the spleen, would the lymph nodes be expected to decrease in size?

DR. BOTTOM: Occasionally such a response is seen.

DR. ALEXANDER: What has been your experience, Dr. Reinhard, in this regard?

DR. REINHARD: I agree with Dr. Bottom. If x-ray is directed to large lymph nodes, they will decrease more rapidly and to a greater extent than if the therapy is directed, for example, to the abdomen, but they usually decrease to some extent even if they are not subjected to direct radiation.

DR. ALEXANDER: You have used radio-active phosphorus in a large number of cases. Do you feel that it should have been used in this patient?

DR. REINHARD: Radio-active phosphorus could have been used, but if reduction in the size of specific lymph nodes or the spleen is the prime objective of therapy, x-ray is preferable.

DR. ALEXANDER: Would you comment on the use of other isotopes?

DR. REINHARD: With the information available to date, I do not believe that any other isotopes have any real advantage over x-ray therapy or radio-active phosphorus.

DR. ALEXANDER: Would you comment on the duration of lymphatic leukema. Does the prognosis vary with age?

DR. REINHARD: In general, the course of chronic lymphatic leukemia in older patients is more benign than it is in patients in the younger age group. The former are more likely to have evidence of the disease as indicated by peripheral lymphadenopathy for a considerable period of time before general systemic effects are noted, and after the diagnosis is made, the older patients survive for a longer period of time. The average duration of life in patients between the ages of twenty and fifty is approximately three years. In a patient over sixty the predicted duration is about four years.

DR. ALEXANDER: Would you comment on the duration of life in myelogenous leukemia?

DR. REINHARD: With the most successful treatment the average course of the disease covers three and one-half years; without treatment the duration is three years. It is important, however, to emphasize that adequate therapy increases the period of useful activity greatly; that is, the patients remain essentially symptom-free until very near the time of death.

DR. C. V. MOORE: I think that Dr. Reinhard's estimate for the average duration of life in myelogenous leukemia was too short. Patients with myelogenous leukemia may live for ten years; this summer Dr. John Lawrence told me that in his experience the average duration of life for patients with myelogenous leukemia, treated with radio-active phosphorus is now over four and one-half years and he thinks that ultimately such patients may be expected to survive for more than five years.

DR. REINHARD: My estimate was based on results in patients with both acute and chronic myelogenous leukemia.

DR. ALEXANDER: Dr. Moore, would you comment on chronic lymphatic leukemia occurring late in life.

DR. C. V. MOORE: Patients with chronic lymphatic leukemia may live for twenty years; such instances are the exception rather than the rule. Dr. Lawrence's

statistics for duration of life in chronic lymphatic leukemia averaged about six years; our results have not been so favorable.

DR. ALEXANDER: Approximately four and one-half months before his death, this man noted dyspnea on exertion and soon thereafter became orthopneic. Dr. Smith, do you believe that these symptoms arose because of cardiac insufficiency?

DR. JOHN R. SMITH: Certainly cardiac disease is the most common cause of dyspnea and orthopnea.

DR. ALEXANDER: When the patient was examined in the clinic, his heart was not enlarged, the sounds were of good quality and there were no murmurs. Unfortunately no blood pressure reading was recorded. The chest x-ray showed no cardiac enlargement. Do you think those findings are compatible with a cardiac basis for the dyspnea and orthopnea?

DR. SMITH: Yes.

DR. ALEXANDER: With x-ray therapy, apparently all of the patient's symptoms improved and he did fairly well until one week before death when he had substernal distress and a rapid progression of the cardiac symptoms—dyspnea, orthopnea and edema. Dr. Massie, what is your interpretation of that sequence of events.

DR. EDWARD MASSIE: Two possible causes for the symptoms seem plausible; either the patient had a myocardial infarction or he developed a pericardial effusion.

DR. ALEXANDER: Do you believe that the dyspnea and orthopnea which the patient had before he received x-ray therapy were suggestive of cardiac insufficiency.

DR. MASSIE: No, I believe that they more likely were based on an extracardiac factor.

DR. ALEXANDER: What extracardiac causes would you consider?

DR. MASSIE: Either pulmonary infiltration or severe anemia could have been responsible for the symptoms. In this case the anemia was only slight and therefore I would consider pulmonary infiltration as the major factor.

DR. ALEXANDER: Do you believe that the x-ray film indicated sufficient pulmonary infiltration to give rise to dyspnea and orthopnea?

DR. MASSIE: No, I do not. However, I have seen, on occasion, patients who presented themselves because of dyspnea and orthopnea and although careful study revealed no cardiac cause of the symptoms, eventually a blood dyscrasia was uncovered as the basis of the symptoms.

DR. ALEXANDER: Dr. Moore, what is your experience?

DR. C. V. MOORE: Dyspnea and orthopnea on the basis of pulmonary infiltration is rare, even in cases in which there is also marked involvement of the mediastinum.

DR. REINHARD: I agree with Dr. Moore. It should be pointed out, however, that in lymphatic leukemia the myocardium may be heavily infiltrated with abnormal cells.

DR. ALEXANDER: Do you believe that the patient improved after his x-ray therapy because of the destruction of abnormal cells in the myocardium.

DR. REINHARD: I do not know.

DR. ROBERT A. MOORE: Heavy pulmonary infiltration in blood dyscrasias is rare. Likewise infiltration of the myocardium to a marked degree is not common. Infiltration of the endocardium with abnormal cells, however, is a common manifestation of leukemia.

DR. ALEXANDER: Dr. Massie, is bundle branch block usually attributed to coronary-artery disease?

DR. MASSIE: Yes. In this case, however, the pain in the left chest may have been associated with pericarditis or pericardial effusion rather than with coronary insufficiency. The bundle branch block may have been existent for many years and its presence in a single electrocardiogram would not

allow one to differentiate between coronary-artery disease and pericardial disease as the cause of the chest pain.

DR. ALEXANDER: This patient developed progressive exophthalmos and a tremor of the hands; on physical examination a nodule was felt in either lobe of his thyroid. No basal metabolic rate was recorded. Dr. Futcher, do you believe that histologic evidence of hyperthyroidism will be found by the pathologists?

DR. PALMER H. FUTCHER: It has been pointed out frequently that the symptoms of hyperthyroidism are often present in leukemia. It has been suggested by one writer that thyrotoxicosis and leukemia both may arise from stimulation of the sympathetic nervous system and he has treated leukemic patients with iodine in the hope of controlling the course of the disease. I should like to ask Dr. Moore how often a hyperplastic thyroid is found in leukemia.

DR. C. V. MOORE: I cannot answer that question, Dr. Futcher. I have always assumed that the increased metabolic rate in leukemia was related to the number of abnormal cells circulating rather than to the thyroid gland *per se*.

DR. ALEXANDER: The question arises as to whether this patient had a bloody pericardial effusion. The physical signs were classical of those seen in pericardial effusion.

DR. MASSIE: I agree that blood was probably present in the pericardium.

DR. FUTCHER: I believe that a more likely explanation is that the needle was in the ventricle.

DR. ROBERT J. GLASER: When we saw this patient, the clinical picture was thought compatible with pericardial effusion and cardiac tamponade, and because of the patient's critical condition, pericardial paracentesis was considered justified. The needle was inserted very slowly but at no time was resistance encountered to suggest that the needle had pierced the ventricular muscle. As soon as bloody fluid was obtained, the procedure was terminated and cell counts were done. The counts indicated that pure blood had been withdrawn.

DR. ALEXANDER: Are there possibilities other than that the ventricular cavity was entered?

DR. W. BARRY WOOD, JR.: Rupture of the auricle or ventricle could explain a bloody pericardial effusion.

DR. ALEXANDER: Yes, the patient may have had a myocardial infarction one week before entry when he first complained of substernal pain with subsequent rupture at the site of infarction.

DR. WOOD: It is also possible that there was pericardial infiltration by leukemic cells with a secondary bloody effusion. Such a finding is not uncommon when carcinoma extends to the pericardial sac.

DR. ALEXANDER: Dr. Moore, is pericardial infiltration and a bloody pericardial effusion common in leukemia?

DR. C. V. MOORE: I do not know, Dr. Alexander. However, Dr. John Tinsley told me of a case report describing infiltration of the auricular wall in leukemia with subsequent rupture and cardiac tamponade. In another case the aortic wall was infiltrated with leukemic cells and subsequently ruptured.

DR. ALEXANDER: It is said that invasion of the pericardium by lymphomas is rare.

DR. R. A. MOORE: I have seen it in a few cases, and in some of these, bloody pericardial fluid was present.

DR. ALEXANDER: The physical findings certainly suggested a pericardial effusion. The heart was tremendous and the signs were classical.

DR. C. V. MOORE: Dr. Robert Moore mentioned that lymphomas may involve the pericardium. I have seen that happen with lymphosarcoma or with Hodgkin's disease, but I do not understand its occur-

rence in lymphatic leukemia. Pleural effusion and ascites are not uncommon in lymphatic leukemia and yet in such instances involvement of the serous membrane with abnormal cells is not found.

DR. R. A. MOORE: I was speaking primarily of lymphosarcoma but occasionally pericardial involvement is seen with leukemia.

DR. GLASER: I should like to justify the use of lanatoside C here. Because of the character of the fluid obtained on pericardial tap, it was concluded that the patient had cardiac dilatation rather than pericardial effusion, and because nothing else seemed to offer any hope, rapid digitalization was attempted.

DR. WOOD: The decision to digitalize this patient was motivated somewhat by a previous experience in which a similar problem faced the staff when a pericardial tap was attempted and blood was obtained. A diagnosis of cardiac dilatation was made in that instance, the patient was digitalized and responded dramatically. It was believed in the present case that digitalis should not be withheld. If the diagnosis of pericardial effusion could have been substantiated, lanatoside C would not have been given.

DR. ALEXANDER: In summary, it is clear that this patient had chronic lymphatic leukemia. The etiology of his heart disease cannot be definitely established; pericardial effusion is apparently ruled out leaving as the most likely possibility coronary artery disease or thyrotoxic heart disease. The patient very possibly had thyrotoxicosis although, as has been pointed out, leukemia and thyrotoxicosis have certain clinical features in common.

CLINICAL DIAGNOSIS: Chronic lymphatic leukemia and cardiac insufficiency due to either coronary artery sclerosis or thyrotoxic heart disease complicating hyperthyroidism.

PATHOLOGIC DISCUSSION

DR. FRANK VELLIOS: At the time of autopsy, the veins of the face and neck were markedly distended and there was edema of the lower extremities. One thousand cc. of fluid were present in the peritoneal cavity, 150 cc. in the right pleural cavity and 300 cc. in the left pleural cavity. The pericardial sac contained 50 cc. of serosanguineous fluid. The heart weighed 700 Gm. and was large, pale and flabby. Near the tip of the left ventricle there was a needle puncture which extended into the cavity. All four chambers were greatly dilated but the ventricular walls were not particularly thickened. The right ventricle measured 5 mm. in thickness, the left, 14 mm. The coronary arteries showed a few arteriosclerotic plaques but none of these encroached upon the lumina of the vessels. The thyroid gland weighed 28 Gm. A small, firm, encapsulated nodule was present in the left lobe; in the right lobe there was a cyst, 1.5 cm. in diameter, containing yellow material. The lungs weighed 2,300 Gm. and were large and firm. The liver weighed 2500 Gm. and was large, firm and purple in color. The spleen, which weighed 900 Gm., was firm and red. The kidneys were not remarkable. Petechiae and ecchymoses were present in the serous membranes.

DR. R. A. MOORE: To answer the questions outlined in the discussion, let us first consider the problem of the hematologic disease. On the basis of the gross observation of enlarged lymph nodes, splenomegaly, hepatomegaly, petechiae and ecchymoses in a number of organs, the diagnosis of chronic lymphatic leukemia can be confirmed.

To turn to the cardiac disease, it was noted that the heart was hypertrophied and dilated. Either valvular disease or hypertension could have explained the heart findings but the absence of changes in

the kidneys would effectively rule out the latter and no valvular abnormalities were noted. The 50 cc. of pericardial fluid was slightly blood-tinged, but other than the identification of the site of the needle puncture in the ventricular wall, there was no evidence of any significant sequellae of the pericardial paracentesis. Attention should be called to the fact that in the laboratory ventricular puncture is a common procedure which is almost always innocuous.

During the clinical discussion the question as to whether the pulmonary infiltration was responsible for the cardiac symptoms was raised, but this explanation must be rejected because the hypertrophy and dilatation involved not only the right ventricle but also the left, and indeed the left ventricular involvement was more marked. No lesion was found in the lung either grossly or microscopically to have accounted for the cardiac symptoms. The amount of coronary artery disease was insignificant. Only a few plaques were found in the vessels and these did not significantly impinge on the lumina. Anemia should be considered as an explanation for dilatation and hypertrophy of the heart, for 50 per cent of patients with pernicious anemia exhibit hypertrophy of the myocardium without apparent cause other than the anemia. In such instances, however, fatty degeneration is found and the classical "tigered" papillary muscles are seen. Another possible cause of cardiac disease is the lesion called Fiedler's myocarditis or isolated myocarditis. These diagnoses must be based on microscopic findings and will be considered subsequently. One must consider the possibility of thyrotoxic heart disease in view of the presence of an adenoma in the thyroid gland. The lesions noted in the gross, however, would not be expected on microscopic study to give evidence of thyrotoxicosis. The histopathologist finds it difficult to correlate gross and microscopic findings in such an instance as this. Other improbable causes of the cardiac findings include so-called beriberi heart and radiation effect. When a sufficient dose of radiant energy is directed to the heart, the myocardium may be injured and feasibly such changes might lead to dilatation and hypertrophy. This patient, however, did not receive radiation to the cardiac area and that possibility must be excluded.

DR. WOOD: Would you comment on leukemic infiltration of the myocardium as a cause for hypertrophy and dilatation of the heart?

DR. R. A. MOORE: The microscopic sections did not show any such infiltration. Figure 1 shows a section of the capsule of a lymph node. The lymphoid tissue is depleted and the cells, which are all of the lymphoid series, may be identified as leukemic cells. There is infiltration in the capsule and in the perilymphatic fat. A section of the lymph node (Fig. 2) shows total destruction of the normal architectural pattern. The cells are all small and uniform in appearance and thus are typical of those seen in chronic lymphatic leukemia.

In the next section (Fig. 3), taken from the bone marrow, there are a few foci of active erythropoiesis but most of the marrow is occupied by leukemic cells of the lymphoid type; there is a decrease in the number of myeloid elements. In Figure 4, a section of the bone marrow under higher magnification shows typical small lymphocytes. The next section (Fig. 5) is from the liver and shows a small amount of leukemic infiltration in the portal spaces and passive congestion of the central areas. The sinusoids are greatly dilated and there is compression and necrosis of the liver cells in the central portions of the lobules. Figure 6 is from the spleen and shows a large follicle. The white pulp is markedly increased in

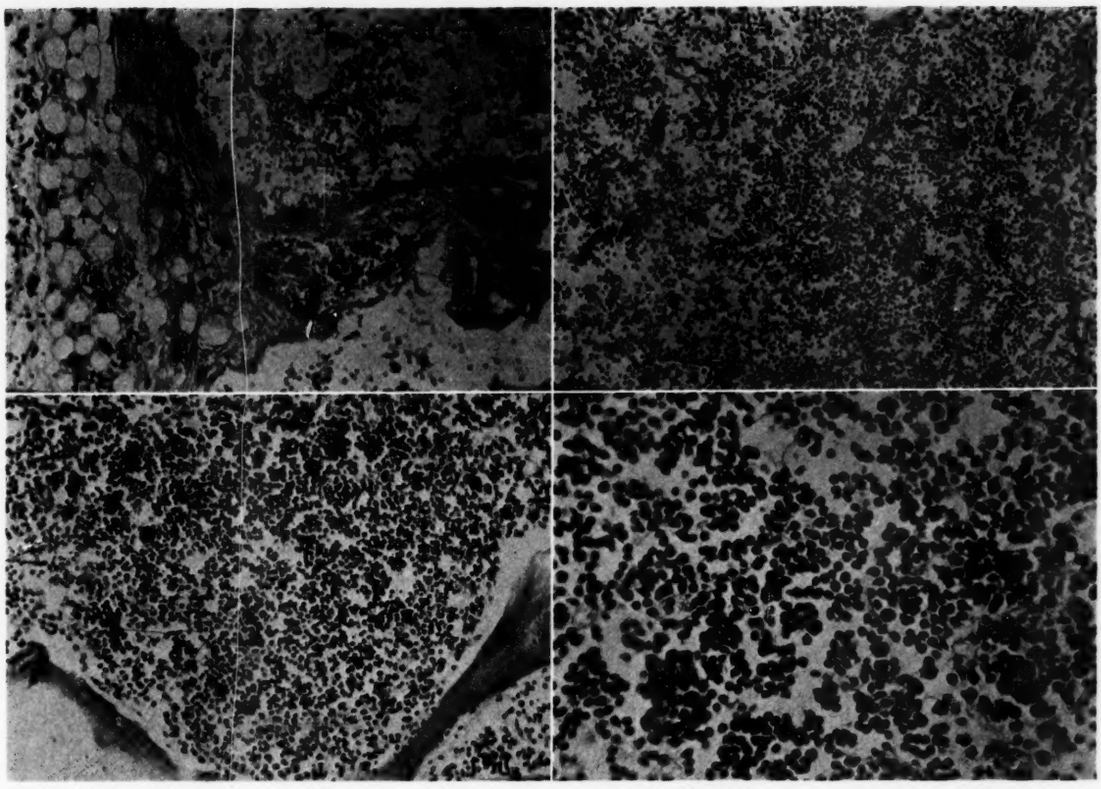


FIG. 1. Section of the periphery of a lymph node showing infiltration of the perilymphatic fat with leukemic cells. × 47.

FIG. 2. Section of the same lymph node showing destruction of the normal architectural pattern by leukemic cells. × 47.

FIG. 3. Section of bone marrow which shows leukemic infiltration. × 47.

FIG. 4. High power view of same section seen in Figure 3. There are a few foci of erythropoiesis but leukemic cells predominate. × 100.

amount because of the presence of leukemic cells and there is a relative decrease in the red pulp. From these microscopic sections the diagnosis of chronic lymphatic leukemia can be substantiated, and from an anatomic standpoint the disease would appear to have been under good control at the time of death for infiltration into the various organs was not massive.

In a section of the thyroid gland (Fig. 7), it is noted that the cells are cuboidal or flat, but the tall columnar cells, which are usually but not invariably associated with hyperthyroidism, are not seen. Occasionally cuboidal cells apparently are present in hyperthyroidism. There is no totally satisfactory method of correlating the clinical picture with the histologic findings in the thyroid gland. A section from the edge of the adenoma (Fig. 8) shows a number of small acini which are relatively free of colloid and it is seen that the acini are apparently isolated in rather acellular interstitial tissue. These are the characteristics of a fetal adenoma. There is no way to decide definitely whether or not the adenoma was toxic.

Figure 9 shows a typical section from the myocardium. The appearance suggests old destruction of some of the myocardial fibers and there is an actual increase in the amount of interstitial tissue. In the next section (Fig. 10) another region is seen in which edema and recent hemorrhage into the tissue are conspicuous. Whether these findings can be attributed to the digitalis

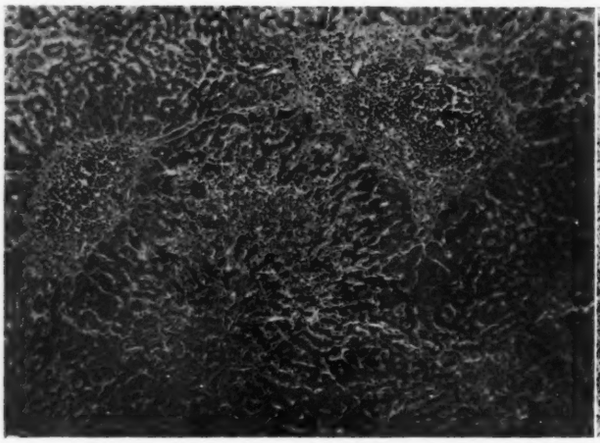


FIG. 5. Section of the liver which shows leukemic cells in the portal spaces and central necrosis. × 47.

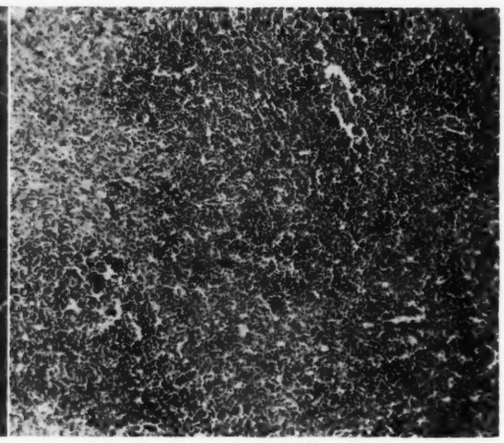


FIG. 6. Section of the spleen showing characteristic changes of chronic lymphoid leukemia. × 47.

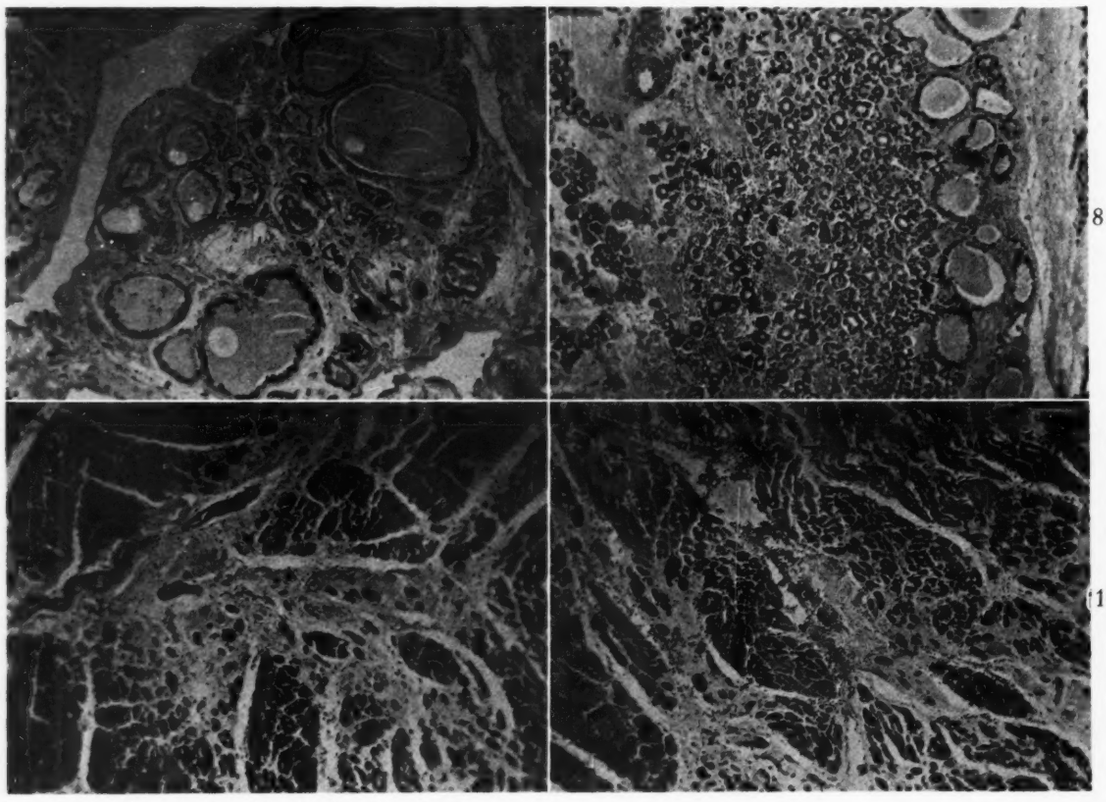


FIG. 7. Section of thyroid gland. No tall columnar cells are apparent. × 47.

FIG. 8. Section from the fetal adenoma of the thyroid. The acini are small and contain little colloid. × 47.

FIG. 9. Section of the myocardium showing increase in the amount of interstitial tissue. × 47.

FIG. 10. Another section of the myocardium which shows edema and hemorrhage. × 47.

glycoside cannot be stated. Occasionally such lesions are noted in the heart muscle of patients who have received a large amount of digitalis.

Returning to the differential diagnosis, many of the suggested possibilities must be excluded on the basis of the microscopic findings. Fiedler's myocarditis is characterized by considerable cellular infiltration, usually lymphocytes and eosinophiles, and such a diagnosis is not tenable here. Had a basal metabolic rate been determined, the existence of thyrotoxic heart disease could better have been established. It is true that in hyperthyroidism destruction and fibrous replacement in the myocardium is seen. Radiation effect and beriberi heart disease seem very unlikely.

DR. WOOD: It was recently brought to my attention that investigation by radiologists has indicated that the myocardium is one of the most radio-resistant organs in the body and that the amount of x-ray necessary to cause myocardial damage is tremendous. For this reason it would appear to me that a diagnosis of thyroid heart disease is much more likely in this case.

DR. R. A. MOORE: Unfortunately, the diagnosis of thyrotoxic heart disease cannot be made without qualification, but it is certainly suggested by a process of elimination.

DR. WOOD: In thyrotoxicosis there is stimulation of the entire lymphatic system which is well recognized clinically. The possibility that the onset of the patient's lymphatic leukemia may have had some relation to the thyrotoxicosis must be considered. Dr. Moore, would you comment on this possibility.

DR. C. V. MOORE: The possible relationship of lymphatic leukemia and thyrotoxicosis has been mentioned in the discussion, and it is true that on occasion total removal of the thyroid has been done in an attempt to alter the course of lymphatic leukemia. The operation has never been successful, however, and more recently the treatment of lymphatic leukemia with thiouracil has not been of value.

DR. FUTCHER: Differential diagnosis of arteriosclerotic and thyroid disease is often difficult and whenever a patient has cardiac enlargement, the basal metabolic rate should be determined.

DR. REINHARD: In this instance a basal metabolic rate would not have been particularly helpful since a reading of +40 to +60 could easily have been attributed to the leukemia.

DR. R. A. MOORE: In summary, from the gross and microscopic findings in this case, the diagnosis of chronic lymphoid leukemia is confirmed; the disease was well controlled at the time when the patient died. Although hyperthyroidism and associated thyrotoxic heart disease cannot be established without equivocation, the anatomic findings are compatible with those diagnoses.

Final Anatomical Diagnoses: Chronic lymphoid leukemia; fetal adenoma and cyst of the thyroid; hypertrophy and dilatation of the heart; chronic passive congestion of the lungs, liver and spleen; hydrothorax, bilateral, and ascites.

Case Report

Permanent Heart Block Following German Measles*

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CARDIAC complications of German measles are rare. In a review of sixty-six years of medical literature, we were unable to find a report of a case of permanent auriculoventricular heart block following German measles. Temporary heart block following German measles and measles has been reported.[1,2,3] We are reporting a case of auriculoventricular heart block discovered by electrocardiographic examination in a previously healthy young physician three weeks after an attack of German measles. The permanency of the block permitted studies of the effects of prostigmin, atropine and quinidine upon the electrocardiographic pattern.

CASE REPORT

A physician, aged twenty-six years, was examined on December 1, 1944, complaining of a rash on the neck and chest, sore throat, and tender nodes in the occipital area, and in the lateral and posterior regions of the neck, all of which had been present for two days.

The history revealed no previous illness, excepting an occasional upper respiratory infection. Examination revealed a generalized papular and morbilliform rash of the neck and chest, slight pharyngitis, and tender lymphadenopathy of the mastoid, cervical and occipital regions. The temperature was 99.6°F., the pulse rate was 88 per minute, and the blood pressure was 122/78. There were no abnormal physical findings; there were no detectable abnormalities of the heart and there were no Koplik spots.

The laboratory examination revealed a white blood count of 8,800, a red blood count of 5,370,000, and a hemoglobin of 15 Gm. (97 per cent). The differential white blood count was normal. The Kahn reaction of the blood was negative. The urine was normal. Two months after the onset, the heterophile agglutination test showed a normal reaction.

The rash disappeared within five days, at which time the temperature became normal. The infection subsided without further incident, except that the patient complained of weakness and a slow pulse rate. Three weeks after the onset (December, 1944) an electrocardiographic examination revealed a 2:1 auriculoventricular block with sinus arrhythmia. Further inquiry into the patient's history at this time revealed no preceding illness. A report from a university health service revealed that in March, 1940, the patient's pulse rate was 78 per minute, and there were no abnormal heart findings. The roentgen examination of the chest was negative.

At weekly intervals, the patient was given quinidine, prostigmin and atropine, and the effects of these drugs upon the block were observed by electrocardiography.

After taking an electrocardiogram (Classical leads I, II, III, aVl, aVf, and aVr, and multiple chest leads CF_{1-6} (Fig. 1A) the patient was given 0.8 Gm. of quinidine sulfate orally. Two hours later, another tracing was taken, (Fig. 1B) and it was noted that the chief effects consisted of an acceleration of the average rate from 72 to 8[illegible] per minute, with a slight increase in the amplitude of the P-waves.

One week later a similar study was conducted using 1 mg. of prostigmin methylsulfate (Neostigmin)* intramuscularly. Subsequently, using

*This material supplied by Hoffmann-La Roche Company.

* From the Department of Medicine, The University of Chicago Medical School.

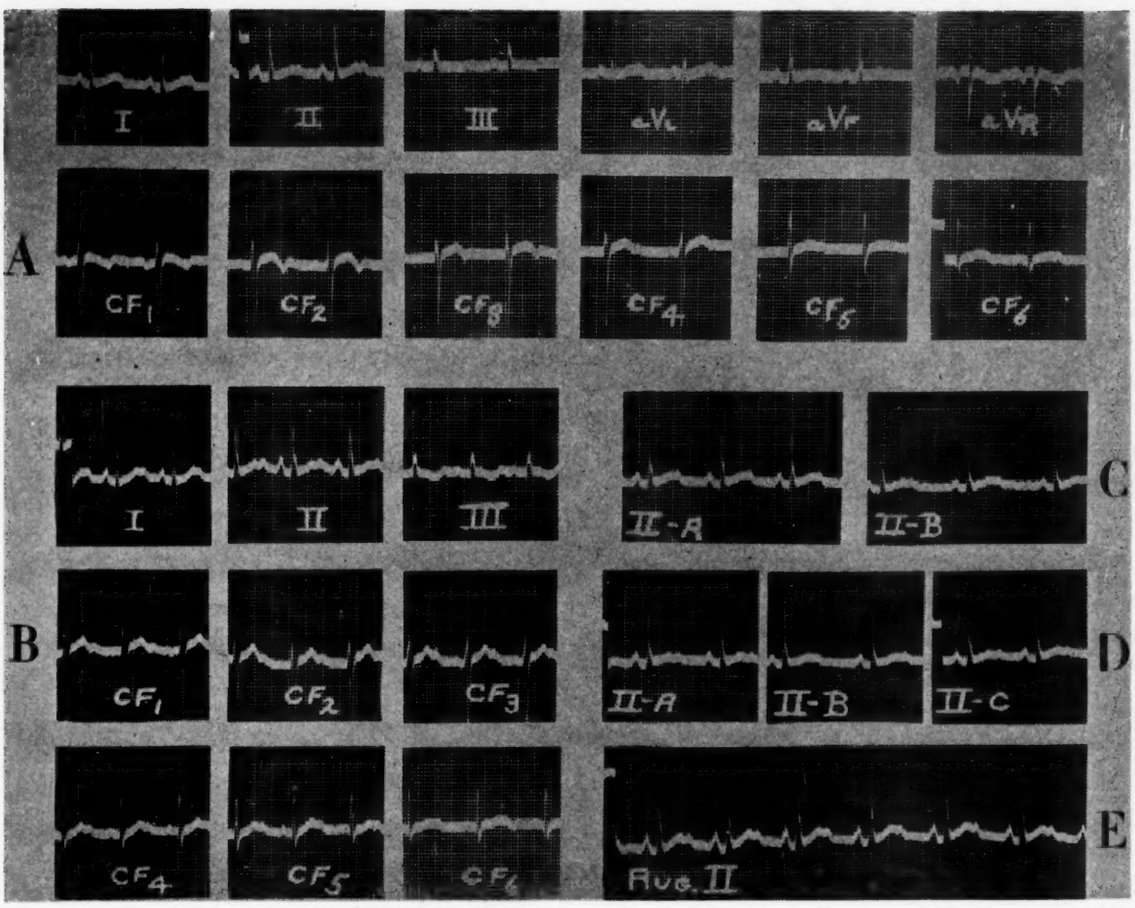

FIG. 1. A, Preliminary electrocardiographic study using classical leads I, II, III; unipolar extremity leads AVL, AVF, AVR; and multiple precordial leads CF_{1-6}, which preceded the drug studies. Average rate of 72 per minute. B, two hours after oral dose of 0.8 Gm. of quinidine sulfate. Average rate of 88 per minute, using classical leads I, II, III, and CF_{1-6}. C, II-A. Classical lead II preceding intramuscular injection of 1 mm. of prostigmin. Average rate of 73 per minute. II-B. Classical lead II, twenty-five minutes after injection of prostigmin. Average rate of 59 per minute. D, II-A. Classical lead II preceding subcutaneous injection of atropine sulfate 0.0013 Gm. Average rate of 79 per minute. II-B. Classical lead II taken fifteen minutes after the injection of atropine. Average rate of 61 per minute. II-C. Classical lead II taken forty minutes after the injection of atropine. Average rate of 78 per minute. E, aug. II. Classical lead II with augmented voltage demonstrating fusion of T and P waves.

classical lead II, tracings were taken at five-minute intervals for forty-five minutes. The average rate was slowed from 73 to 59 per minute with the maximum effect at 25 minutes after the injection, (Fig. 1C) which was in close accordance with previous findings.[4]

Atropine sulfate, 0.0013 Gm., was injected subcutaneously and again using classical lead II, tracings were obtained at five minute intervals for forty-five minutes. The average rate was slowed from 70 to 61 per minute within fifteen minutes after the injection, (Fig. 1D) and at forty minutes after the injection, the average rate was accelerated to 78 per minute. (Fig. 1D.)

Subsequent electrocardiograms revealed that the block persisted in 2:1 rhythm with mild sinus arrhythmia. A tracing (Fig. 1E) using doubly augmented voltage demonstrated fusion of the T and P waves.

COMMENTS

Most of the textbooks of medicine, cardiology, electrocardiography and most of the reports in the literature in their discus-

sion of heart block do not mention measles or German measles as etiological factors, but they do mention other etiological factors such as rheumatic fever,[5,6,7,8] diphtheria,[7,9] congenital deformities of the septum,[10] uremia, asphyxia, syphilis, influenza,[11,12] scarlet fever, streptococcic infections, typhoid fever,[13] typhus fever, tonsillitis,[14,15] pneumonia,[16] excessive vagal stimulation,[17] coronary diseases,[18] secondary tumor growth[19] and various toxic agents.

The earliest comments concerning heart block due to measles were made at the turn of the century in 1903 by Burzi,[1] who described a case of complete auriculoventricular heart block with low pulse rates and Morgagni-Adams-Stokes seizures, occurring as an attack of measles was receding. The heart block was transient and the patient recovered fully.

Zahorsky,[2] in 1905, described a case of "cardiac asthenia" due to measles, but this article is not accessible, and it could not be determined whether this case did or did not have heart block.

Logue and Hanson[3] recently reported a case of temporary complete heart block due to German measles which occurred during the pre-eruptive stage. The administration of atropine sulfate decreased the degree of block from 3:2 rhythm to 1:1 rhythm.

Stein and Uhr,[10] in reporting a case of congenital heart block, did not consider it significant that the child had had German measles sixteen months prior to detection of the block, although on three earlier examinations no comment concerning abnormalities of the heart was recorded.

Eyster and Middleton,[7] reporting auriculoventricular heart block in children, mentioned one case wherein "measles and 'inflammation of the heart valves,'" preceded the examination.

White[20] does not consider atropine worthwhile in permanent 2:1 heart block, and it was ineffective in the case we are reporting. (Fig. 1D.)

SUMMARY

1. A case of permanent 2:1 auriculoventricular heart block following German measles is reported.

2. A review of the literature revealed no similar case report, although reference was made to two cases of temporary heart block following measles.

3. The effects of the following drugs were noted through electrocardiography: (1) The average rate was accelerated from 72 to 88 per minute at two hours after the oral administration of 0.8 Gm. of quinidine sulfate. (2) The intramuscular injection of 1 mg. of prostigmin slowed the average rate twenty-five minutes later from 73 to 59 per minute. (3) Atropine sulfate 0.0013 Gm., injected subcutaneously, slowed the average rate within fifteen minutes from 70 to 61 per minute, and forty minutes after the injection the average rate accelerated to 78 per minute.

REFERENCES

1. Burzi, G. Bradicardia da miocardite acute morbillosa. *Gazz. d. osp.* 24: 1256, 1903.
2. Zahorsky, J. A case of cardiac asthenia following measles. *St. Louis Courier Med.*, 33: 86, 1905.
3. Logue, B. L. and Hanson, J. L. Complete heart block in German measles. *Am. Heart J.*, 30: 205, 1945.
4. Goldfinger, D. and Wosika, P. H. Electrocardiographic effects of prostigmin. *Am. J. M. Sc.*, 212: 418, 1946.
5. Peabody, F. W. Heart block associated with infectious diseases. *Arch. Int. Med.*, 5: 252, 1910.
6. Murray, I. Rheumatic manifestations following rubella. *J. Roy. Army M. Corps.*, 76: 48, 1941.
7. Eyster, J. A. and Middleton, W. S. Auriculoventricular heart block in children. *Am. J. Dis. Child.*, 19: 131, 1920.
8. Mosler, E. Wirkung einer akut fieberhaften Erkrankung auf einen bereits vorhandenen totalen Herz Block. *Klin. Wchnschr.*, 57: 181, 1920.
9. Stecher, R. M. Electrocardiographic changes in diphtheria; complete auriculoventricular dissociation. *Am. Heart J.*, 4: 545, 1929.
10. Stein, W. and Uhr, J. S. Congenital heart block; case. *Brit. Heart J.*, 4: 7, 1942.

11. Cockayne, E. A. Heart-block and bradycardia following influenza. *Quart. J. Med.*, 12: 409, 1919.
12. Taub, S. J. Heart block following grippe infection. *Illinois M. J.* 49: 497, 1926.
13. Dossen, R. Atypical typhoid fever; heart block; myocarditis post-typhosa (Romberg); value of the atropine test. *Am. J. M. Sc.*, 186: 499, 1933.
14. Humphrey, T. F. and Ekermeyer, E. W. Rubella—report of epidemic with unusual number of complications and relapses. *Ohio State M. J.*, 33: 406, 1937.
15. Hutcheson, J. M. Heart block in mild infections. *South. Med. & Surg.*, 86: 475, 1924.
16. Shaw, H. W. German measles and its complications. *J. Indiana M. A.*, 29: 229, 1936.
17. Weiss, S. and Ferris, E. B. Jr. Adams-Stokes syndrome with transient complete heart block of vaso-vagal reflex origin. *Arch. Int. Med.*, 54: 931, 1934.
18. Salcedo-Salgar, J. and White, P. D. The relationship of heart-block, auriculoventricular and intraventricular, to clinical manifestations of coronary disease, angina pectoris, and coronary thrombosis. *Am. Heart J.*, 10: 1067, 1935.
19. Percy, C. B. and Rogers, H. Lymphangio-endothelioma of heart causing complete heart block. *J. Path. & Bact.*, 39: 281, 1934.
20. White, P. D. Heart Disease. 3rd Ed., p. 939. New York, 1944, The Macmillan Co.

Editorial

The Dangerous Carrier of Hemolytic Streptococci

Among the most important problems in the field of communicable disease is that of the mode of spread of streptococcal infection. Little information concerning the origin of sporadic cases or of epidemics has been available. It is known that the carrier rate of Group A hemolytic streptococci is high when an epidemic of scarlet fever or streptococcal sore throat is occurring, but a high carrier rate does not necessarily result in an epidemic. The real significance of the high carrier rate was brought out by Schwentker[1] in his study of scarlet fever at Fort Warren, Wyoming, where he found that the greatly increased incidence of Group A streptococcus carriers which occurred in those companies exhibiting a high morbidity of scarlet fever was due to the epidemic strain, Type 19. But what initiates such an epidemic, *i.e.*, what constitutes the conditions which give rise to the initial cases has, up to the present, not been understood.

An observation made by Gordon[2] a number of years ago gave a clue to the elucidation of this problem. He found that scarlet fever patients who had had a complicating sinusitis or rhinitis were much more prone to cause secondary cases of scarlet fever after leaving the hospital than were the usual run of convalescents from this disease. The significance of this observation was not appreciated, probably because of the undeveloped state of the subject at that time. It was not until the recent war that further rapid progress in the understanding of the mechanism of transmission of streptococcal infection was made. The studies of Hamburger and associates, working under the Commission of Air-Borne Infections of the U. S. Army Epidemiological Board, clarified many little understood problems in this field and culminated in the discovery of the dangerous carrier of hemolytic streptococci.

The initial stimulus leading to their investigations was the finding that in certain hospital wards housing common respiratory disease the presence of Group A hemolytic streptococci in the throats of as many as 50 per cent of the patients resulted in no cases of streptococcal disease or of non-symptomatic infection of other patients, whereas in another ward a single carrier of one of these same types of streptococci might give rise to a number of cases of streptococcal infection. A second observation of importance was that when blood agar settling plates were put on each bedside table in a ward of scarlet fever convalescents, the number of hemolytic streptococci recovered from the air was consistently greater day after day beside one or two patients.[3] This lead to an intensive study of the environment of such patients and it was found that their bedding, clothing and the floor dust about the bed were much more heavily contaminated with streptococci (of the type

[1] Schwentker, F. The relation between scarlet fever morbidity and streptococcus carrier rates. *Am. J. Hyg.*, 38: 207–210, 1943.

[2] Gordon, J. E. Epidemiology of scarlet fever. A clinical approach. *J. A. M. A.*, 98: 519–523, 1932.

[3] Hamburger, M. Jr., Puck, T. T., Hamburger, V. G. and Johnson, M. A. Studies on the transmission of hemolytic streptococcus infections. III. Hemolytic streptococci in the air, floor dust, and bedclothing of hospital wards and their relation to cross infections. *J. Infect. Dis.*, 75: 79–94, 1944.

present in the throat) than were the environments of the other ward patients. It was then discovered that the individuals who produced such marked contamination of their surroundings were those carrying hemolytic streptococci in their noses.[4] Quantitative studies of the dispersal of streptococci by throat carriers on the one hand, and nasal carriers (who almost always had positive throats also) on the other, showed that the nasal carrier dispersed 80 to 100 times as many streptococci as did the individual carrying these micro-organisms in the throat but not in the nose. Nasal carriers of hemolytic streptococci were found most commonly among convalescents from streptococcal disease but a considerable number appeared quite well and gave no history of infection although an analysis of this latter group by means of antistreptolysin titers of the blood serum indicated that most of them represented missed cases.[5] Further studies showed that blowing the nose and sneezing produced the greatest dispersal of streptococci from the nasal carrier and that contamination of the hands, particularly from the nose-blow, constituted the principal means of conveying streptococci to the immediate environment.[6]

Direct evidence that such carriers were dangerous came from an epidemiological study of cross infections in hospital wards and cases occurring in barracks.[7] Nearly all the hospital cross infections were traced to a single nasal carrier who exhibited a high "streptococcal output" while other carriers on the same ward putting out relatively small numbers of streptococci, with one exception, failed to spread infection. Similarly, outbreaks of streptococcal disease in barracks were traced to a single nasal carrier of the type causing the infection. This aspect of the study was amplified by Loosli, Lemon and co-workers,[8] also working under the Commission on Air-Borne Infections, to include the pattern of streptococcal contamination of the environment in relation to spread of disease among the occupants of the barrack. The most striking example of the menace presented by the nasal carrier dispersing large numbers of hemolytic streptococci came from the study of a food-borne epidemic of Type 1 streptococcal infection involving more than 100 convalescent patients who ate in the hospital mess.[7] The outbreak was traced to a "cold food handler" with strongly positive nose and throat cultures and tremendous contamination of the hands. The probable vectors were salad and pie which he sliced and wrapped separately "to keep each piece clean."

In an attempt to clear up the nasal carrier state, groups of such carriers were treated by Hamburger and Lemon[9] with sulfadiazine and penicillin. The most promising results came from the use of calcium penicillin in beeswax-peanut oil in a daily dosage of 300,000 units. Streptococci disappeared from the nose and throat shortly after beginning treatment and did not return in half the cases following cessation of the drug. Due to insufficient supply, it was not possible to continue treatment for more than five days.

[4] Hamburger, M. Jr., Green, M. J. and Hamburger, V. G. The problem of the "dangerous carrier" of hemolytic streptococci. I. Number of hemolytic streptococci expelled by carriers with positive and negative nose cultures. *J. Infect. Dis.*, 77: 68–81, 1945.

[5] Lemon, H. M. and Hamburger, M. Jr. Missed cases and contact carriers among nasal carriers of beta hemolytic streptococci. *J. Immunol.*, 54: 189–196, 1946.

[6] Hamburger, M., Jr., Green, M. J. The problem of the "dangerous carrier" of hemolytic streptococci. IV. Observations upon the role of the hands, of blowing the nose, of sneezing and of coughing in the dispersal of these microorganisms. *J. Infect. Dis.*, 79: 33–44, 1946.

[7] Hamburger, M. Jr., Green, M. J. and Hamburger, V. G. The problem of the "dangerous carrier" of hemolytic streptococci. II. Spread of infection by individuals with strongly positive nose cultures who expelled large numbers of hemolytic streptococci. *J. Infect. Dis.*, 77: 96–108, 1945.

[8] Loosli, C. G. and Lemon, H. M. Unpublished work of the Commission on Air-Borne Infections.

[9] Hamburger, M. Jr., and Lemon, H. M. The problem of the "dangerous carrier" of hemolytic streptococci. III. The chemotherapeutic control of nasal carriers. *J. A. M. A.*, 130: 836–841, 1946.

These studies have contributed most important knowledge concerning the manner in which streptococcal disease is spread and point out the direction in which rational control may proceed. While it may not be wise at the present time to neglect the non-nasal throat carrier entirely, it seems quite evident that the nasal carrier of hemolytic streptococci provides the chief source of infection and that effective control of such carriers would constitute a long step forward in reducing the incidence of this disease. This knowledge should also be most helpful in resolving the confusion of the present quarantine regulations which keep scarlet fever patients isolated for varying periods of two to three weeks and ignore cases of naso-pharyngitis due to the same micro-organism.

O. H. Robertson, M.D.

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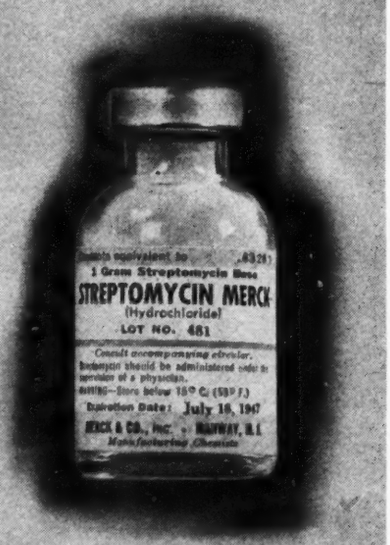

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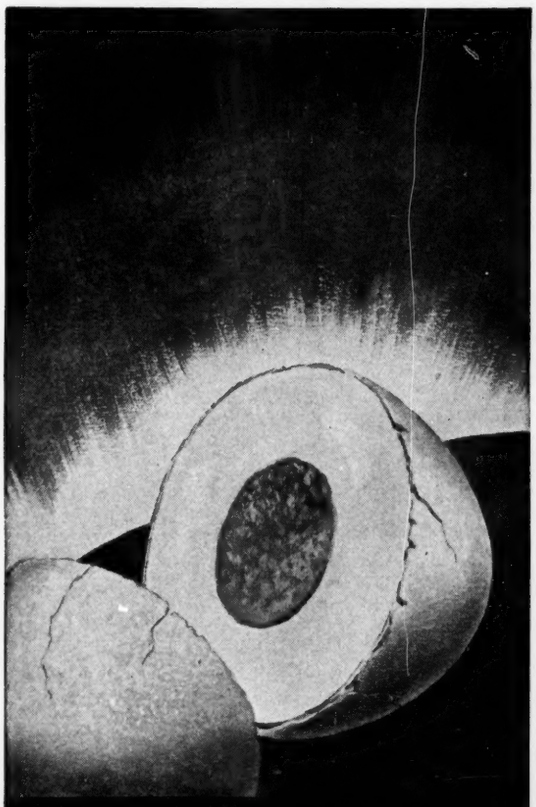

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1. Steck, I. E.: Clinical Experience in the Treatment of Arthritis with Massive Doses of Vitamin D, Ill. Med. J., *71*:243 (March) 1937.

2. Traeger, C. H., Squires, W. H. and Rudd, E.: Therapeutic Value of Electrically Activated Vaporized Ergosterol, Indust. Med., *14*:202 (March) 1945.

3. Levinthal, D. H. and Logan, C. E.: The Orthopedic and Medical Management of Arthritis, Journal Lancet, *63*:48 (Feb.) 1943.

4. Horwitz, H. and Joseph, N. R.: Prolonged Observation on a Group of Arthritic Patients, Indust. Med., *15*:100 (Feb.) 1946.

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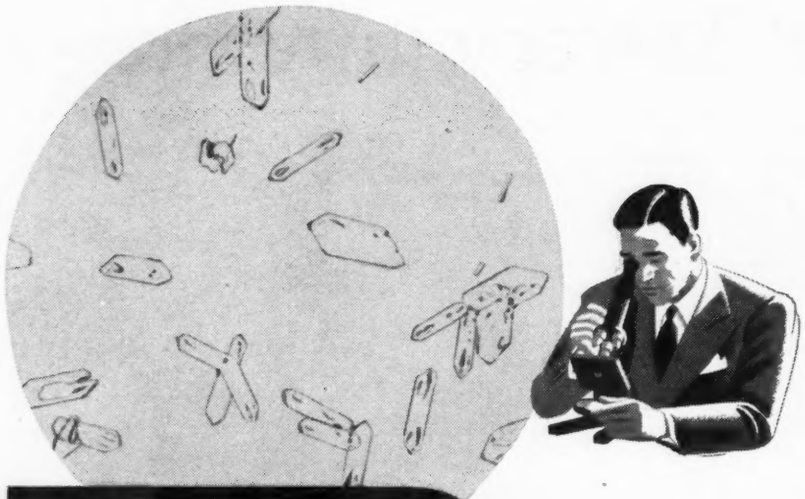
5. Livingston, S. K.: Vitamin D and Fever Therapy in Chronic Arthritis, Arch. Phys. Therapy, *17*:704 (Nov.) 1936.

6. Snyder, R. G., Squires, W. H., Forster, J. W., Traeger, C. H. and Wagner, L. C.: Treatment of Two Hundred Cases of Chronic Arthritis with Electrically Activated Vaporized Sterol, Indust. Med., *11*:295 (July) 1942.

7. Farley, R. T.: The Treatment of Arthritis with Massive Dosage Vitamin D, J. Am. Inst. Homeop., *31*:405 (July) 1938.

8. Snyder, R. G., Squires, W. H. and Forster, J. W.: A Six-Year Study of Arthritis Therapy—with Special Reference to the Pharmacology, Toxicology and Therapeutics, Indust. Med., *12*:291 (May) 1943.



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*Lehr, D.: Proc.Soc.Exper.Biol.& Med. *58*:11 (Jan.) 1945

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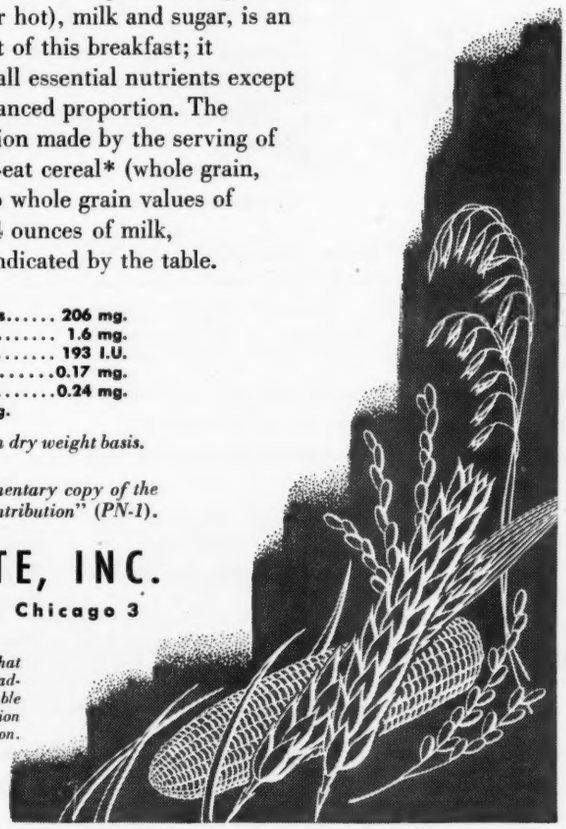

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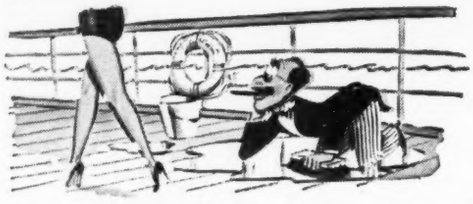

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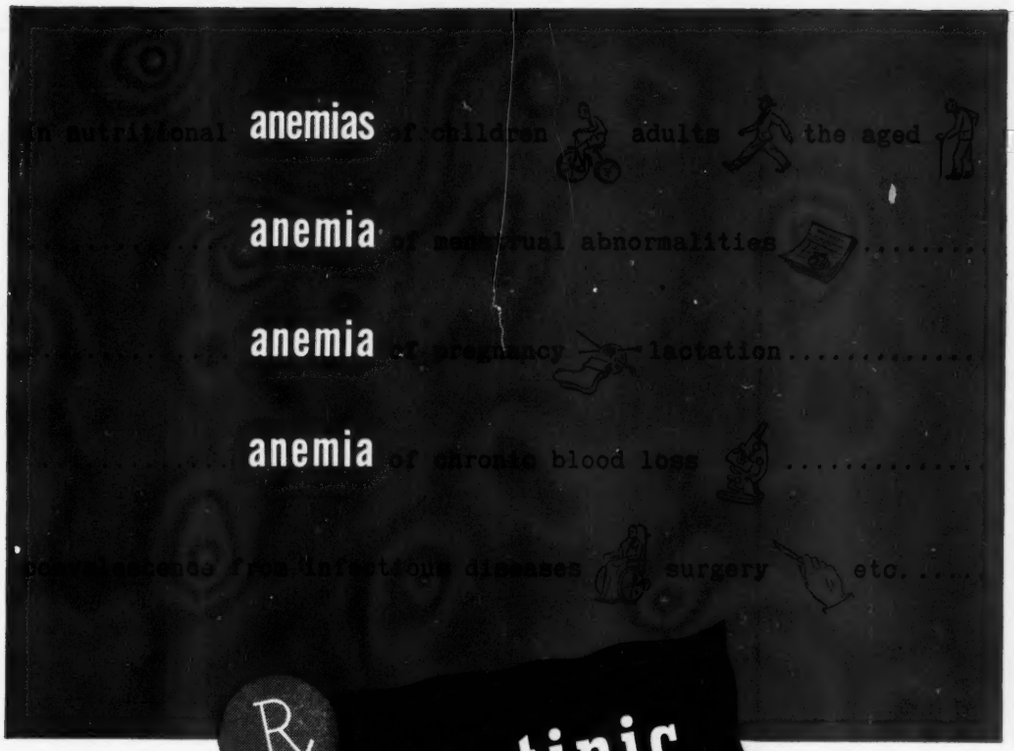

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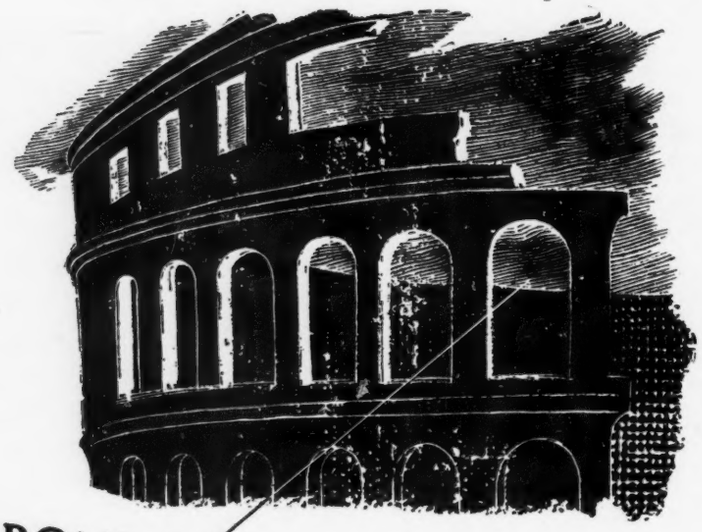

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